



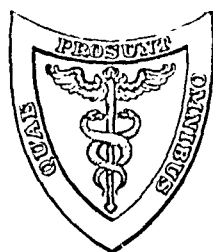
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ORIGINAL ARTICLES.

CARCINOMA OF THE PANCREAS.\*

By KELLOGG SPEED, M.D.,  
CHICAGO, ILLINOIS.

ALONG with our increase in knowledge of upper abdominal disease obtained from observation in the operating room and surgical research, we have made intense study of the gall-bladder and gall-ducts in the last few years. As more intimate knowledge of the anatomy and physiology became accepted, observers began to study the pancreas, especially in its inflammatory reactions and their relation to gall-tract disease. Very recently Deaver, Flexner, Opie and others have assumed that many of the pancreatic inflammations can be traced to lymphatic extension by continuity from the inflamed gall-tract glands or lymphatics. We have also learned by experiment and clinical observation that bile forced into the pancreas by way of its ducts may set up pancreatitis. When gall-stones or gall-bladder inflammation are present we can anticipate finding infections of varying virulence, and pancreatitis has become one of our every-day diagnoses in the upper abdomen. Formerly we thought little of this gland from a surgical diagnosis standpoint except in those rare instances of fulminating attacks of pancreatitis generally recognized when an acute abdomen was opened and the pathognomonic spots of fat necrosis were found on the omentum and peritoneal surface. We now know also that ligation of the pan-

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creatic ducts does not lead to fat necrosis of either the organ itself or the abdominal contents. Retention of the secretion which must follow is cared for by absorption into blood and lymph streams and the pancreatic ferments are rendered harmless.

Carcinoma of this organ has, of course, been studied and several series of cases been reported in the past. In the light of our progress in upper abdomen pathology and diagnosis it seemed that a study of pancreatic cancer might be of some value in furthering knowledge of this interesting gland. My interest has been sharpened by five patients of my own suffering from this disease and I have collected the statistics of the instances of cancer of the pancreas in the County Hospital, Chicago, occurring in the last six years. Altogether I have tabulated 52 cases of primary pancreatic cancer. Over half of these were clinical diagnoses made by the responsible attending staff of the hospital.

In the 52 cases at hand the average age at the time of diagnosis of primary cancer was 57 years, the youngest was 36 years, the oldest 76. Primary carcinoma of this organ has been found in an infant of 2 years by Herringham among the 17 cases occurring in St. Bartholomew's Hospital in 11 years. He found an average of five men afflicted to 1 woman; our series gives 36 males to 16 females.

In a series of cases collected by Herringham from the literature, the duration of the disease from the time of its recognition in 20 patients was not longer than 4 months; 33 of our patients died in the hospital, with an average stay of but 22 days. The average time of onset of symptoms before hospital admission was a few weeks, in some instances but a few days.

The most constant symptom found in our series is cachexia. This was present in 90 per cent. of the patients at time of admission and involved a weight loss of a few pounds to 80 pounds. This symptom appears to be very important; the loss is so rapid and unremitting that the disease should be suspected whenever rapid reduction in weight is mentioned by the patient. Its cause may be the loss of fats in the stools, a marked anorexia which most cases suffer, hemorrhages or a great distaste for fats commonly manifested. Because such a small percentage of these patients showed glycosuria, and as acetone and oxybutyric acid are so rarely found in the disease, the loss of weight cannot be attributed to excess oxidation in the tissues.

In order of frequency the next common symptom is jaundice, which occurs before the patient seeks medical advice, and is often the symptom which alarms him. Once inaugurated it is progressive and extreme, presenting all the symptoms of an intense cholemia. We found it in 80 per cent. of the cases on admission. Rarely an anomalous course of the common duct may account for absence of this finding.

Pain is the third prominent symptom, usually of cardialgic or gastralgalic character, present in 61 per cent. of the admissions. The

pain is frequently colicky at first and is often felt just preceding the onset of jaundice. We may imagine that the compression in the common duct by the cancer in the pancreatic head produces this obstructive jaundice and the backed-up bile distends gall-tracts and gall-bladder, with resulting colic. I recall one case of pancreatic cancer seen during my internship in the County Hospital in which the gall-bladder was extremely dilated and its peristaltic contractions could be seen through the emaciated abdominal wall. After a few weeks the pain becomes duller in character, may be gnawing, is quite constant and is frequently referred to the back. Those patients operated on for relief of the jaundice recovered from this pain in a large proportion.

Personal knowledge on the patient's part of an abdominal tumor mass or its discovery on examination was the next common finding in order; 55 per cent. of our patients had a mass either in the liver or some part of the midepigastrie region. Most frequently this mass was liver enlarged by bile or metastases or the overdistended gall-bladder. In a small percentage of patients the tumor was felt in the pyloric region and was the pancreas itself or an extension of its cancer into the stomach or the neighboring organs. The pancreatic mass is not moved by respiration; it lies behind the inflated stomach or colon and was felt best after abdominal tapping in those patients who presented ascites.

Ascites was present in approximately 20 per cent. of the patients, as was also hemorrhage, which occurred in 11 patients, 2 of the mouth, 4 of the nose, 1 of the bowel, 2 in the buttocks and skin and 2 of the stomach. Hemorrhages within the alimentary tract or abdomen are most often caused by pressure of glands or carcinoma, varices resulting which burst. Malignant ulceration is also found as a cause. Skin hemorrhages are found most often in those patients with fat necrosis; the removal of calcium which combines with the fatty acids acting with jaundice causes blood changes which result in hemorrhage. Our patients did not show petechiæ, which are mentioned as a prominent finding in the disease. One instance of ascites was a pure chylous ascites caused by pressure stenosis of the receptaculum chyli from enlarged glands.

Constipation was mentioned in 19 of the 52 patients; diarrhea occurred in but 3.

Edema of the lower extremities occurred in 6 per cent. of the patients. Both ascites and extreme edema are caused by pressure, except a few instances of carcinomatosis of the peritoneum.

Gastro-intestinal roentgen-ray examination was made of 23 patients and a correct diagnosis was arrived at in but 2, the fluoroscopic and plate examination showing little positive findings except displaced stomach or intestine with no obstructions or filling defects.

The urine of 3 of these patients showed sugar and one showed acetone. Bile, of course, was found in all the jaundiced patients.

The feces were not always examined. They showed blood in 30 per cent. of the total number of cases and excess free fat in 15 per cent. The stools were frequently bulky from fat and undigested material.

Stomach analyses were also not always possible, but in the 26 patients examined, 21 showed a normal or slightly increased acidity while 5 had a reduced amount of acid. The motor power and digestion of the stomach were usually good.

Steatorrhea, or the finding of excess fat in the stools, was not a constant nor reliable symptom. I refer to it only to mention that physiologically an individual may excrete up to 20 per cent. of all ingested fat and still be within normal limits. Likewise azotorrhea, or the finding of undigested proteid material, usually meat fibers, is inconstant and unreliable. We know that whenever the bile is taken away from the intestinal contents at the ampulla of Vater or in acute diarrheas there follows disturbance of fat digestion and absorption. If, however, a patient with or without jaundice shows both steatorrhea and azotorrhea it is highly presumptive that the external secretion of the pancreas is failing. These symptoms are also late in the course of the disease.

Various laboratory tests have been announced which have been claimed as pathognomonic for primary pancreatic cancer. The elaborate Cammidge test and the Loewi test of adrenalin in the conjunctival sac have both been proved erroneous. No pathognomonic pancreatic symptomatology can be expressed because the disease of this organ is too often overshadowed by symptoms of involvement of the neighboring structures, stomach, duodenum, gall-tracts and colon.

Of our cases 11 went to autopsy. The head of the pancreas is most often involved in cancer, the body next and the tail least often. Not one showed pancreatic calculus. Stone has been considered an exciting cause of gall-tract carcinoma. There are a few cases in the literature of pancreatic stone associated with primary cancer of the pancreas. If carcinoma is confined entirely to the tail and left side of the body and does not involve the common bile duct by pressure, we may find no symptoms at all until the patient is near the end and emaciation and extensive metastases are in evidence.

Our autopsy records show that metastases are usually first in the lymphatic glands around the pancreas and gall-tract areas. The liver, of all neighboring organs, is most often invaded. The stomach, colon, spleen, kidneys, and thoracic organs may be involved. One of our cases showed carcinomatous involvement of the eighth dorsal vertebra, one a chylous ascites, and several a general carcinomatosis of the peritoneum, abdominal and thoracic organs.

The common gall-duct is embraced completely in the head of the pancreas in 62 per cent. of human cadavers; in the remainder it lies in a deep groove in the head of the gland. Consequently cancer of

the pancreatic head involves the common duct by pressure, with resulting jaundice and gall-bladder dilatation. High intestinal obstruction, pyloric obstruction, large bowel obstruction, thrombosis of the mesenteric vessels and resulting bowel gangrene, aneurysm of the aorta or external pancreatic fistula may be found. We can understand that when the two ducts of the pancreas are occluded the disturbance of digestion from lack of the three ferments secreted by the pancreas will follow, but every cancer will not involve the head and the two ducts, hence the symptoms are variable. Likewise it has been found, on microscopic examination, that there is great and true hypertrophy of the cells of the islands of Langerhans, which may explain the infrequency of glycosuria as found in this series. Those islands remaining uninfluenced by the carcinomatous process take on extra duty and maintain a carbohydrate equilibrium by their increased internal secretion. Functional disturbance of the pancreas is not evidenced until the greater portion of the gland is affected. Usually if diabetes has developed the surgeon is too late to offer assistance.

Wright found accessory pancreas near the umbilicus in connection with the persisting remains of the vitelline duct. An accessory pancreas may account for lack of glycosuria and also for the development of primary cancer. These accessory glands have been found by or inside of the duct of Santorini, in the walls of the stomach, duodenum, jejunum or ileum, with small independent ducts opening into the contiguous bowel.

Pathologists have had some discussion over the cell origin of pancreatic cancer. Finding the greatly enlarged and heavily staining cells of the island of Langerhans misled them into believing that these cells may be those forming the cancer (Fabozzi). It was supposed that glycosuria was so seldom present because the cancer cells, taking their origin from the island of Langerhans, retained their power of forming an internal secretion which controlled carbohydrate metabolism. To distinguish between primary carcinoma of the duodenum and bile ducts histological study is necessary. Ewing says that carcinoma of the pancreatic ducts follows periductal fibrosis and carcinoma of the parenchyma appears after interstitial fibrosis. Two types of cells are found: one cylinder-celled adenocarcinoma arising from the ducts as papillary outgrowths and second, carcinoma simplex, arising from the parenchyma, usually scirrhus in type.

Surgical treatment is difficult to apply to patients suffering with carcinoma of the pancreas. The anatomical position of the gland, while quite accessible, is one which invites disaster to proximal organs and structure if pancreatectomy is performed. Cysts and encapsulated tumors of the pancreas have been successfully removed by either the abdominal or lumbar route, but I have not found in the literature successful complete pancreatectomy in cancer of the

pancreas. Some operators have considered that they have performed complete pancreatectomy, but autopsy has disproved their belief. Partial pancreatectomy can be successfully done. We must recall that a large percentage of these patients are deeply jaundiced. Blood coagulation time is greatly increased, up to eight or even ten minutes, so that operative procedures are hazardous. The leaking of pancreatic secretion after operation into the abdominal cavity always results in death. Exudate from the injured pancreas, which is not the normal secretion, prevents the formation of salutary peritoneal adhesions, and catgut stitches are rapidly digested. Pancreatic juice mixed with blood is very toxic, and when introduced into the peritoneal cavity will cause death without the aid of bacterial infection. We must also remember the anatomical relation of the common duct, stomach, aorta, colic arteries, duodenum, large bowel, kidneys and spleen.

Palliative treatment is possible. To relieve the backing up of gall we can drain the gall-bladder. Patients do poorly after this operation and usually die within a few weeks. Cholecystgastrostomy returns the bile to the intestinal tract, as also does cholecystenterostomy. I prefer the latter, because if the gall-bladder is connected to the stomach, pyloric or duodenal obstruction may arise from pressure or extension of the cancer, and then a gastroenterostomy would be needed in addition. All these operations are represented within this series. Thirteen of our patients were operated on, mostly for gall-bladder drainage or removal; 4 of these were later examined at autopsy. At this time I have one patient with primary carcinoma of the pancreas alive four months after a cholecystenterostomy. The gall-bladder is usually so large, grape fruit size or larger, that it is not difficult to anastomose it to the stomach or intestine.

The matter of diagnosis is most interesting. Of these 52 patients a correct diagnosis was made in only 3 instances when the patient was first examined. Among admission diagnoses were the following: cholelithiasis, cholecystitis, carcinoma of the stomach, cirrhosis of the liver, organic heart disease and pulmonary tuberculosis.

In all patients with a deep jaundice, with cachexia or obscure upper abdominal symptoms, when a positive diagnosis cannot be made, we should consider the pancreas, and especially carcinoma, in those of mature age when there is no history of gall-stones or previous febrile attacks. If the gall-bladder is enlarged, with or without changes in the liver size, if there are tumor masses, or any of the other symptoms enumerated, we are probably dealing with the pancreas.

Also, I believe when we are performing operations in the gall-tracts or pyloric region we should always palpate this deeper lying organ. Several of the patients in this series were operated on for removal of the gall-bladder without investigation of the pancreas. The true.

condition was revealed at autopsy. The gall-bladder removal takes away our best means of offering palliative treatment, because there then cannot be performed any circuiting operation to keep the bile within the individual's alimentary tract, and failure from continuous bile drainage is rapid. When the bile is returned to the intestines we may see a temporary gain of weight and strength and some prolongation of life, an extension of a few months or a year. There is, moreover, no mussy bilious fistula which requires constant attention; the patient can be up and about with a closed abdomen.

#### ANATOMIC DIAGNOSES IN ELEVEN POSTMORTEMS.

1. Hammond. Date of autopsy, March 30, 1915. Examiner, Bissell. Carcinoma of the pancreas and stomach; generalized metastatic carcinomatosis of the peritoneum; marked emaciation; ascites; therapeutic paracentesis middle puncture wound of the abdominal wall; moderate edema and passive hyperemia of the lower lobe of the right lung; compensatory marginal emphysema of the left lung; moderate fatty changes in the myocardium, liver and kidneys; cloudy swelling of the liver and kidneys; multiple retention cysts of both kidneys; right-sided obliterative fibrous pleuritis; moderate edema of the cerebral cortex; hyperplasia and anthracosis of the tracheobronchial lymph glands; missing teeth.

2. David Rhodes. Date of autopsy, June 2, 1915. Examiner, Wells. Primary carcinoma of the pancreas, with extensive secondary involvement of the retroperitoneal thoracic lymph glands, with extension into the stomach, ileum and cecum, with secondary ulceration; massive secondary in omentum, metastases in liver and lungs, parietal and visceral pleura, diaphragm, adrenals, perirenal tissues and subcutaneous tissue and spleen and myocardium; senile arteriosclerosis; parenchymatous nephritis; ascites; edema of lower extremities; pseudomelanosis of the intestines; edema of the lungs; calcification of the trachea and bronchi.

3. Herman Strehlow. Date of autopsy, August 3, 1916. Examiner, Nuzum. Primary carcinoma of the pancreas; metastatic carcinoma of the retro-aortic, iliac, lumbar and mesenteric lymph glands; carcinomatosis of the peritoneum; pressure stenosis of the receptaculum chyli at the level of the second and third lumbar vertebræ by hyperplastic cancerous lumbar lymph glands; true chylous ascites; marked pressure stenosis of the pyloric sphincter of the stomach by the carcinomatous pancreas; chronic dilatation of the stomach; varicosity of the veins of the cardiac orifice of the esophagus; free tarry black blood in the stomach and bowel; emaciation; compensatory varicosity of the superficial veins of the chest, abdomen and the right thigh; bilateral hydrohemothorax; marked edema and passive hyperemia of the lungs; latent healed and encapsulated fibrous apical tuberculosis; right-side focal adhesive pleuritis;

tuberculous cervical adenitis; ancient healed surgical incisions of both sides of the neck; fatty changes in the myocardium and liver; terminal edema of the scrotum and lower extremities; gold capped tooth; work-worn hands.

4. Andrew Nikolick. Date of autopsy, November 9, 1916. Examiner, Nuzum. Primary carcinoma of the head of the pancreas; metastatic carcinomatosis of the liver, left lung, pericardial sac, ribs and lymph glands generally; icterus; clay-colored stools; frank lobar pneumonia of the right upper lobe (gray hepatization); section wound in hollow of right arm; work-worn hands.

5. Susie Magree. Date of autopsy, June 13, 1913. Examiner, Harms. Carcinoma of the pancreas, with metastases in the liver; mitral insufficiency; hypostasis of the lungs.

6. Luke Moore. Date of autopsy, April 6, 1917. Examiner, Nuzum. Primary carcinoma of the pancreas; metastatic carcinomatosis of the perigastric, biliary and peribronchial lymph glands; secondary carcinoma of the liver, lungs and adrenals; marked varicosity of the esophageal veins at the cardiac orifice of the stomach; ruptured esophageal vein; free and clotted blood in the stomach and small bowel; marked anemia; icterus; ascites; marked passive hyperemia and edema of the lungs; missing teeth.

7. Murray Catlin. Date of autopsy, August 28, 1917. Examiner, Le Count. Primary carcinoma of the body of the pancreas; secondary metastatic carcinoma of the liver, peritoneum and bowel; ulcerative carcinoma of the liver, peritoneum and bowel; ulcerative carcinomatous enteritis; edema evacuo (carcinomatous cachexia) of the subpericardial adiposæ tissue; pressure kinking of the splenic artery (carcinoma); mural thrombosis of the splenic vein; infarction of the spleen; marked anemia; moderate emaciation; sordes of the lips; chronic diffuse nephritis; secondarily contracted kidneys; submucous fat infiltration of the renal pelves; arteriosclerosis of the aorta and front mitral leaflet; fibrous myocarditis; brown atrophy of the myocardium; senile emphysema of the lungs; barrel-shaped chest; patent foramen ovale; hypertrophy of the left heart; huge edema of the leptomeninges; disseminated atrophy of the cerebral cortex; foramen magnum pressure furrow of the brain stem; marked hypostatic hyperemia and edema of the lungs; lessened yellow material of the adrenal glands; slightly fatty liver; fatty changes of the lining of the aorta and carotid arteries; epicardial fat infiltration of the heart; fibrous pleuritis; calcification of the tracheobronchial lymph glands; small traction diverticulum of the esophagus; external fibrous epicardial patch; fibrous adhesions between the right lobe of the liver and the fatty capsule of the right kidney; ossified costal and thyroid cartilages and falx cerebri; arcus senilis; marked coal-dust pigmentation of the lungs and tracheobronchial lymph glands; nodular glandular hyperplasia of the prostate gland; plaques jaunes of the left frontal lobe of the cerebrum; cavities;

absence of some teeth (caries); circumcised penis; hairy body; pigmented mole of the trunk; scar of the skin of the left knee; post-mortem digestion of the lining of the esophagus.

9. John Hermanson. Date of autopsy, May 10, 1918. Examiner, Davis. Primary carcinoma of the head of the pancreas; generalized icterus; biliary cirrhosis of the liver; clotted blood in the large and small bowel; marked anemia; bile staining of the kidneys; right-sided obliterative fibrous pleuritis; hypertrophy of the heart; slight senile arteriosclerosis; fibrous adhesions between the gall-bladder and the liver; left-sided inguinal hernia; calcification of the thyroid cartilage; superficial healing abrasion of the right elbow; fibrous adhesions between the greater omentum and the parietal peritoneum anteriorly; carious teeth.

10. Sam Rhys. Date of autopsy, June 25, 1918. Examiner, Nuzum. Primary carcinoma of the head of the pancreas; dilatation of the common, cystic and hepatic ducts; cholelithiasis; moderate icterus; moderate tawny yellow atrophic cirrhosis of the liver; slight diffuse nephritis; acute vegetative endocarditis of the aortic valve; marked senile disseminated arteriosclerosis; sclerosis of the aortic and mitral valves; sclerosis of the coronary arteries; caseous tuberculosis of the upper lobe of the right lung; healed bilateral apical tuberculosis; bilateral apical fibrous pleuritis; fibrosis and hyperplasia of the peribronchial lymph glands; right inguinal hernia; carious and missing teeth.

11. Frank Turanek. Date of autopsy, September 14, 1918. Examiner, Nuzum. Primary medullary carcinoma of the head of the pancreas; secondary carcinomatosis of the peripancreatic, perigastric and retroperitoneal lymph glands; secondary carcinoma of the bile ducts, gall-bladder and liver; free and clotted blood in the small bowel; hemorrhagic ascites; slight icterus; bile staining of all the viscera of the body; moderate hyperplasia of the spleen; multiple petechial hemorrhages in the renal pelvis; old healed fibrous tuberculosis of the apex of the right lung; latent caseous and calcified tuberculosis of the peribronchial lymph glands; right-sided obliterative fibrous pleuritis; disseminated scratch marks of the skin of the body.

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## THE THERAPEUTIC USE OF OXYGEN.<sup>1</sup>

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OXYGEN has been used as an inhalant occasionally for many years, but its efficacy has always been doubted by many, chiefly on the theoretical grounds that as the oxyhemoglobin of the blood is already nearly saturated, no increase in this can be obtained by the mere raising of the percentage of oxygen in the inhaled air. A further objection has been urged that the oxygen may act as an irritant to the respiratory passages. It may be as well to dispose of this objection at once. It is quite true that if animals be placed for a short time in an atmosphere which contains three atmosphere pressures of oxygen they soon contract pneumonia, and, further, Lorrain Smith has shown that this also occurs if animals are kept for several days in an atmosphere of pure oxygen; but it has also been shown that an atmosphere of pure oxygen can be breathed for

<sup>1</sup> Read before the Academy of Medicine, Toronto, February, 1920.

many hours without any evil effects, and also that, an atmosphere containing under 70 per cent. of oxygen can be breathed with impunity for any length of time.<sup>2</sup> Thus we need have no fear that in giving inhalations of oxygen for ten to fifteen minutes at a time we are running any danger of causing irritation of the air passages.

In recent years much work has been done on oxygen by such men as Haldane and Leonard Hill on the physiological side, and clinically its value has been greatly enhanced by the experience of the War. In the acute respiratory inflammations produced by enemy gas, nothing proved so useful in giving relief as did oxygen. Lately, Dr. Meltzer, of the Rockefeller Institute, has written strongly urging its value in pneumonia. Using a special apparatus, which I will presently demonstrate, he has shown that such cases may not only be symptomatically relieved, but that life may be saved in some apparently hopeless instances.

Looking first of all at the physiological side of the question, it is undoubtedly true that when a healthy individual is breathing quietly the percentage of oxygen in ordinary air (about 20 per cent.) is not only enough to sufficiently saturate his hemoglobin and to supply the needed partial oxygen pressure in his blood plasma (which is about one-fortieth of that of the hemoglobin), but the percentage of oxygen in the inhaled air may be reduced to perhaps 14 per cent. without causing any distress to the patient. In other words, the atmosphere contains a higher percentage of oxygen than is required for the needs of the healthy resting individual. But let that individual exert himself, and soon he will become breathless, and then it is found that an increasing of the oxygen content of the air will help him. This has been abundantly proved by Leonard Hill and others, who have shown that a man can do more physical work without distress if he is breathing an atmosphere artificially enriched with oxygen than if he is depending upon the ordinary air. Evidently the difference between the 14 per cent., which is all the oxygen that a man at rest requires, and the 20 per cent. of the ordinary air is, as Meltzer puts it, a "factor of safety," and while this factor of safety is sufficient for meeting the increased demands of ordinary exertion, it is not enough for emergencies. A man suffering from some interference with his respiration may be likened to the healthy one undergoing extra exertion.

Further, at high altitudes the partial pressure of oxygen may be less than that of an atmosphere containing only perhaps 14 per cent. of oxygen, and here there is no margin of safety, and the least exertion may bring on symptoms of want of oxygen (often very suddenly), and, of course, if a still higher altitude is attained, as is often done by airmen, then these symptoms will come on without any exertion.

<sup>2</sup> Flack and Hill: Text-book of Physiology, p. 304.

Again, it has been found that at altitudes of 6000 feet and over cases of pneumonia do very badly,<sup>3</sup> this factor of safety being now missing. Haldane says here: "Even in ordinary cases of croupous pneumonia the alveolar oxygen pressure may be a matter of decisive importance. This is clearly shown by the fact that these pneumonias do very badly at high altitudes. At Cripple Creek (altitude, 10,000 feet), in the Rocky Mountains I found that this was so well recognized that all cases of pneumonia were put on the train and sent down to the prairie level."<sup>4</sup>

Oxygen is very essential to the living tissues. As a leading writer in the *British Medical Journal* says, "A man may go for weeks without food, for days without water, but for seconds without oxygen."<sup>5</sup>

Anoxemia is the term applied by Haldane to "the condition when the rate of supply of oxygen is insufficient for the normal carrying on of life."<sup>6</sup> The causes of it are four: (1) Defective saturation of the arterial blood with oxygen; (2) slowing of the circulation; (3) defective proportion of available hemoglobin in the blood; (4) an alteration of the dissociation curve of the oxyhemoglobin, so that this gives off its oxygen less easily than usual.

Most of these causes are evident. For example, any decrease in the oxygen pressure in the inspired air, or any interference with the passage of air to the blood from outside, will produce a defective saturation of the arterial blood with oxygen, as will also any increased using up of the arterial oxygen if a new supply be not immediately available.

Slowing of the circulation will tend to anoxemia both by allowing the blood to dwell too long in contact with the tissues and also by delaying its return to the lungs for recharging.

Anemia means a want of hemoglobin in the blood, and poisoning with carbonic oxide gas with nitrites and with arseniuretted hydrogen will prevent the carrying of oxygen by the hemoglobin.

The alteration of the dissociation curve of the oxyhemoglobin is a less evident cause of anoxemia. Bohr, of Copenhagen, showed that if the carbonic acid in the blood be lowered the hemoglobin tends to cling to its contained oxygen, and thus the peculiar condition may exist of an anoxemia with the hemoglobin laden with oxygen which it will not part with.

As regards the relation of anoxemia to cyanosis it may be said that cyanosis always means anoxemia (the hemoglobin being more or less in the form of reduced rather than oxyhemoglobin); but while anoxemia is generally accompanied by cyanosis, this is not necessarily the case: for example, in carbonic-oxide poisoning the blood is cherry red, and yet the patient may die of want of oxygen. Again, when the carbonic acid is deficient, the tissues may be suffering from

<sup>3</sup> Sewall, Henry: Forchheimer's Therapeutics, vol. i, p. 281.

<sup>4</sup> British Med. Jour., February 10, 1917, p. 182.

<sup>5</sup> Ibid., July 19, 1919, p. 81.

<sup>6</sup> Ibid., p. 65.

anoxemia, and yet the blood may be red with hemoglobin, which will not part with its oxygen (according to Bohr's law) because of the lowness of the  $\text{CO}_2$ .

Respiration depends upon two main factors: (1) the presence of sufficient  $\text{CO}_2$  in the blood and (2) a want of oxygen. Normally the  $\text{CO}_2$  in the alveolar air of the lungs is about 5.6 per cent. of this air, and the least rise in this percentage causes such a stimulation of respiration that the percentage is quickly reduced. On the other hand a slight fall causes the condition of apnea, and then in consequence the percentage quickly rises again. The  $\text{CO}_2$  acts through the blood by stimulating the respiratory center.

The effects of fluctuations in the percentage of oxygen in the alveolar air are not nearly so great. Want of oxygen does cause increased breathing, but only to a slight extent. It is possible for a person to be blue from want of oxygen and yet have no increase in respiration if the  $\text{CO}_2$  be lower than it should be. But the respiratory center consists of cells which require oxygen for their proper function, just as do all the cells of the body, and when the oxygen in the inspired air is sufficiently reduced the respiration becomes weak and then fails. As Haldane says, "One of the most important effects of prolonged or extreme anoxemia is a temporary partial failure of the respiratory center, so that oxygen or even artificial respiration may be required for many hours."<sup>7</sup>

I have seen this fact beautifully demonstrated by Professor Macleod in the physiological department of our University, where the tracing of the respiratory movements of an animal deprived of oxygen shows gradual failure which quickly disappears when oxygen is again administered.

It is well to remember that after all it is the amount of oxygen in the blood plasma that really counts. Usually this is only about one-fortieth as much as is contained in the hemoglobin, but as it is used up in the tissues it is constantly replaced from the red cells. Normally, 100 c.c. of plasma contains only about 0.35 c.c. of oxygen in solution, the balance of the oxygen in the blood being combined with the hemoglobin; but it is possible by increasing the oxygen in the inspired air sufficiently to raise the oxygen in solution in the plasma to nearly 3 c.c. per 100 c.c. For example, if the oxygen in the alveolar air be raised to 36.4 per cent., that in the plasma will stand at 0.945 per cent., and if the alveolar oxygen be 86.7 per cent. that in the plasma will be 2.26 per cent. This is always assuming that the pulmonary epithelium is passive. Thus it is possible to increase the partial oxygen pressure in the plasma some seven times by merely raising the percentage of oxygen in the inspired air. After all, the red cells are merely carriers, and it is the oxygen in the plasma that directly feeds the tissues. "One well-known proof

<sup>7</sup> British Med. Jour., July 19, 1919, p. 69.

of this consists in replacing the blood in a frog with physiological saline solution and then subjecting the frog with the saline in its bloodvessels to an atmosphere of pure oxygen, when it will be found that the animal continues to absorb the normal amount of oxygen and exhale the normal amount of  $\text{CO}_2$ . It respire normally without any blood in the bloodvessels."<sup>8</sup> The plasma, like travellers during a strike of railway porters, may to a certain extent do its own carrying.

The effect of anoxemia on the vital tissues is drastic. If the oxygen pressure be low enough then these tissues quickly die; but short of this they may be fatally damaged, as is seen when after CO poisoning an individual may die, although all the CO has again been replaced with oxygen. It is thus important to remember that anoxemia, which clinically is usually shown by cyanosis, is a damaging condition, especially to the nervous and circulatory tissues, and hence should be relieved as quickly as possible, not only for the immediate relief given but also for the sake of the future life and health of these tissues. It has been recently pointed out by Meakins, Priestly and Haldane<sup>9</sup> that in many cases in which the respiration is shallow but rapid the patient is insufficiently ventilating his lungs, although breathing a great deal. Here a vicious circle is liable to be established, the anoxemia making the breathing shallow though rapid and the shallow breathing increasing the anoxemia. Rapid breathing often denotes an insufficient breathing just as a rapid heart may mean a weak heart. Cheyne-Stokes' breathing is a sign of a failing respiratory center and may usually be at least temporarily removed by inhalations of oxygen.

Thus from a clinical point of view, whenever a patient is cyanosed and usually whenever he is breathing very rapidly he is more or less in a state of anoxemia, and we should try to relieve this by increasing the percentage of oxygen in the air that he breathes. Haldane says, "Cyanosis may always be taken as an indication that oxygen inhalation should be considered." There are, of course, two kinds of cyanosis: (1) The leaden color of the skin often seen in acute respiratory conditions, when the oxyhemoglobin is reduced, and yet the veins are not overfull, and (2) the blue color of the mucous membranes, in which the veins are distended with this reduced blood. In this latter type venesection is often called for, followed, if necessary, by oxygen.

**Methods of Giving Oxygen by Inhalation.** I may say here in parenthesis that oxygen has been administered subcutaneously, intravenously and into the cavities of the body, but we are only now dealing with its use as an inhalant. Perhaps the commonest way of giving oxygen is to hold a funnel connected with the oxygen cylinder near to the face of the patient. This is a most unsatisfactory

<sup>8</sup> Macleod's Physiology, p. 378.

<sup>9</sup> Jour. Physiol., 1919, lii, 433.

way and scarcely deserves to be considered as oxygen administration at all. Meltzer has shown that it is not thus possible to raise the percentage of oxygen in the inhaled air by more than 2 per cent. Further, in a patient already short of breath the mere holding of a funnel close to his mouth and nose gives him a sensation of smothering, and he will often try in his agony to remove the apparatus. I have not used the Haldane apparatus, but it involves the placing of a mask over the patient's face, and hence has this objection, and Haldane himself says that the patient may try to remove it. The same objection applies to the apparatus of Leonard Hill. A much better method than this, and the one that we used most extensively overseas, was the giving of the oxygen through a soft rubber tube inserted into one nostril and held in position by a strip of strapping. This is a wasteful way of giving the gas, but very efficient, and the patient does not object. Its efficacy can be greatly increased if an attendant rhythmically closes the opposite nostril during each inspiration.<sup>10</sup>

A third way of giving oxygen is by the use of the oxygen chamber. I saw this method last year at Cambridge, where Dr. Barcroft and his assistants were experimenting with it. They had three chambers in use. These were made specially for the treatment of late gassed cases, but as the Armistice had come before many soldier patients had been treated they were continuing the work on other conditions. The oxygen content of the atmosphere in the chambers was maintained at 40 to 50 per cent., any excess of CO<sub>2</sub> and moisture being removed by suitable agents. The patients were kept in the chambers from 5 P.M. until 10 A.M. next day for five consecutive days. Great improvement in their condition was evidenced by the removal of the nocturnal dyspnea, from which they nearly all suffered, by a greater capacity for physical work during the day and by the removal of the polycythemia, which was usually present. Several British hospitals have had such oxygen chambers erected as part of their equipment, notably at Guy's and at Stoke-on-Trent, and hope is held that many patients will be much benefited by their use. I would like to see one in Toronto.

The last method that I will describe is that of Dr. Meltzer, of the Rockefeller Institute. The apparatus consists of a hollow tongue depressor which is placed in the patient's mouth and is connected with a gas bag filled from an oxygen cylinder. A valve is so placed that during inspiration the oxygen under pressure from the elastic walls of the bag enters the patient's mouth, while during expiration the oxygen flow is checked and a large opening appears near the valve through which the patient exhales. This valve is worked rhythmically.

<sup>10</sup> Using this method with Professor Macleod, we found that his alveolar oxygen was raised to over 20 per cent. when the tube was in one nostril and the other nostril left open, while when the other nostril was rhythmically closed during each inspiration the oxygen in the expired air rose to 50.9 per cent.

cally by the thumb of the operator. By this arrangement the oxygen enters the air-passages under pressure during inspiration, while during expiration no resistance to the outflow of air occurs. Meltzer says<sup>11</sup> that Dr. A. L. Meyer, of the Rockefeller Institute, found that after he had been thus insufflated for eight minutes his expired air consisted of nearly pure oxygen, the nitrogen of the atmosphere being displaced by this gas. Professor Macleod and I tried this on him, and the analysis of his alveolar air after nine minutes' insufflation showed a percentage of oxygen of 34.6 instead of the normal of 16.5, and when we repeated the experiment, with the nose clamped so that he breathed entirely through the apparatus, the percentage of oxygen in the expired air rose to 86.7 per cent., which practically confirms Dr. Meyer's findings. Now, as before stated, a rise of the oxygen pressure in the alveolar air to 36.4 per cent. means a corresponding rise in the oxygen in the plasma to 0.945 per cent., and if the oxygen in the alveolar air stands at 86.7 then that in the plasma will be 2-26, or seven times the normal. The hemoglobin in a healthy man is already nearly saturated with oxygen and will, hence, not take up little more when it is offered to it through the raising of the percentage in the alveolar air. In fact, as already said, the inhalation of oxygen by the resting normal individual produces no results. The pulse-rate, respiration and blood-pressure remain unaltered and the individual has no subjective sensations. But in anoxemia the hemoglobin is not saturated, and in such cases we cannot only raise the oxygen percentage in the blood plasma, but also in the red blood cells, and hence the cyanosis tends to disappear.

Coming now to actual experience in the therapeutic use of oxygen I think that if it be properly given there is no doubt of its value in suitable cases. I say properly given, for if the administration consists in merely holding a funnel connected with the oxygen tank in front of the patient's face then the results will naturally be *nil*. As already said, in this way one cannot raise the oxygen in the alveolar air by more than 2 per cent., and, further, the patient probably objects to the apparatus, which interferes with his normal breathing. When the oxygen is given by the tube in a nostril great relief can usually be given. During the epidemic of influenza and pneumonia in England last year I frequently saw military patients who were breathing badly and cyanosed (even although being treated in the open air) improve visibly in a few minutes under this form of administration. Not only does the cyanosis lessen or disappear and the breathing tend to become slower and deeper, but again and again have I heard the patients express their great satisfaction at the relief given, and in such a definite disease as pneumonia the subjective improvement is of much significance and value. In some cases the cyanosis

<sup>11</sup> The Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, Jour. Am. Med. Assn., October 6, 1917.

is relieved and yet the breathing remains rapid, while in others the opposite is the case; but in most instances the cyanosis is lessened and the respiration slows. Thus in a patient insufflated recently by the Meltzer method the respiration fell from 32 to 18 and the slight cyanosis from which he suffered remained practically unaltered. Professor Hoover has called attention to the frequent dissociation of the anoxemia and cyanosis,<sup>12</sup> but it would serve no useful purpose here to go into details in regard to it. If the pneumonic patient is having much pleuritic pain he will often say that the oxygen has relieved it. I presume that the slowing of the breathing accounts for this.

It may be objected that oxygen insufflation is only symptomatic treatment and that the patient will soon relapse, but very often he may not do so for hours or not at all, and the treatment can always be repeated as required. As Haldane says: "It may be argued that such measures as the administration of oxygen are at the best only palliative, and of no use, since they do not remove the cause of the pathological conditions. As a physiologist I cannot agree with this reasoning. The living body is no machine, but constantly tending to maintain or to revert to the normal, and the respite afforded by such measures as the temporary administration of oxygen is not wasted but utilized for recuperation." It is pleasant to read such belief in the *vis medicatrix naturæ* from such an authority. Meltzer thinks that many patients have the power of storing oxygen in their tissues. This is not, I believe, accepted by physiologists, but the fact remains that the improvement after oxygen insufflation is usually very persistent.

In conclusion, it may be urged that oxygen should be employed in all serious cases of anoxemia and that its administration should not be delayed and only used as a *dernier ressort*, but should be employed early, before the vital tissues have been much damaged by the want of oxygen.

**Conclusions.** 1. Oxygen is of value whenever a state of anoxemia exists. This is universally recognized in cases of mountain sickness and sickness from high flying, and in poisoning by CO, nitrites and arseniuretted hydrogen and also in the effects of enemy gas.

2. For the same reasons oxygen should be tried in all cases of cyanosis, and also in acute respiratory conditions, such as pneumonia, when anoxemia threatens.

3. The ordinary method of giving oxygen by holding a funnel connected with the oxygen cylinder near the face of the patient is practically useless.

4. A better method than this is to give the gas through a rubber tube inserted into one nostril, and this may be made more effectual if the opposite nostril be rhythmically compressed during inspiration, the mouth, of course, being kept closed.

<sup>12</sup> Jour. Am. Med. Assn., September 14, 1918, p. 880.



5. The oxygen chamber is a very effectual way of giving oxygen, especially in chronic cases, but it involves much expense and care.

6. An extremely useful and effectual appliance for the administration of oxygen is Meltzer's apparatus for oral insufflation.

NOTE.—In the *British Medical Journal* March 6, 1920, Dr. J. C. Meakins shows that the arterial blood of the normal individual is nearly 5 per cent. "undersaturated" with oxygen, while in pneumonia the "undersaturation" may amount to nearly 18 per cent. By giving oxygen with the Haldane apparatus he was able to reduce the degree of undersaturation in the normal by one-half and in the pneumonic individual to just over 3 per cent. In other words, by the use of the method he increased the oxygen content of the blood of the cyanosed pneumonic person to above that of the normal individual. No better evidence than this could be needed of the value of oxygen inhalation in anoxemia.

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### A CASE OF SPLENOMEGALY WITH POLYMORPHONUCLEAR NEUTROPHIL HYPERLEUKOCYTOSIS.

By E. L. TUOHY, B.A., M.D.,

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IN the November number, 1919, of this JOURNAL, p. 618, Dr. H. Z. Giffin, of the Mayo Clinic, presented a case of "Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly." As soon as this article appeared I immediately recalled a patient we had treated with curiously corresponding findings: a very large spleen; a very high leukocyte count markedly increasing after splenectomy; a gradual decrease in number thereafter, with marked constitutional improvement. Comparing the two cases the most striking difference appeared in the type of the leukocytes: Giffin's case presented marked and persistent eosinophilia; in our case there was an overwhelming preponderance of mature polymorphonuclear neutrophils. It is suggested to the reader that Giffin's article be reviewed in order to compare the two reports. His thorough search of the literature dealt largely with eosinophil leukocyte increase. It is notable, however, that he found in a thorough search of the literature little at all comparable with his case. I wish to present the following data, acknowledging that I have not consulted the Surgeon-General's Library nor made a thorough review of the literature; but that portion immediately available has shown nothing corresponding whatever except Giffin's report.

CASE HISTORY.—C. D., aged fifty-eight years; female; married; two daughters living and well. She was first seen November 21, 1917.

*Family History.* Negative.

*Past History.* Stated that she had acute arthritis at sixteen, but nothing eventful thereafter until signs of the menopause developed at forty, when she discovered she had uterine prolapse.

*Present Complaint.* On May 3, 1917, she developed severe pain in the left side. The physician who was called stated he found a large spleen. She was in bed four days and thought she had fever. The pain recurred at intervals, and each time she thought fever recurred. Four days before coming to the office she found difficulty in lying down or stooping or making any considerable movement of the body; cough or deep breathing gave much distress. She had lost twenty pounds in weight since the onset of this complaint, but had been up and around doing her work much of the time.

*Physical Findings.* Patient looks thin, tired and in evident distress. A very large tumor was found in the upper left quadrant, extending diagonally downward and toward the right, three inches beyond the navel and having the general characteristics of an enlarged spleen. It was very tender to pressure and the pain increased on movement. No spleen notch could be identified. General examination of the chest was negative. The fluoroscope showed some fixation of the left side of the diaphragm. It also showed the stomach crowded over to the right; the colon was not studied. Pelvic examination uncovered a pessary which she had worn for fourteen years. When this was removed the cervical area looked very angry, and it left some bleeding. Retroperitoneal septic accumulation was thought of, but the temperature was normal and nothing else corroborated such a hypothesis. Furthermore, after three days in the hospital, with vaginal douches, the local condition entirely cleared up. The blood showed a picture strikingly different than might have been expected from a splenomyelogenous leukemia. The first leukocyte count showed 65,000. The blood smears showed an overwhelming predominance of well-formed adult type polymorphonuclear neutrophil cells. After three days' rest in bed and symptomatic treatment the second leukocyte count showed 45,000.

Photomicrographs (Figs. 1 to 3), with lower, medium and higher magnification, show strikingly well the form of the leukocytes. The neutrophil granules took on the customary stain with Wright's stain, but the eosinophils were difficult to find, as were also the small lymphocytes. An average differential count showed: Polymorphonuclears, 99 per cent.; large lymphocytes, 0.5 per cent.; eosinophils, 0.5 per cent.; an occasional normoblast; 200 cells were counted. This relationship continued in all the differential counts made. Red-blood count showed 4,200,000 and hemoglobin 80 per cent. when the patient was first seen.

After continuing, with much discomfort and abdominal distress, operation was advised and carried out by Dr. W. A. Coventry, of this clinic, on December 3, 1917:

"A large spleen was found, strongly adherent to the diaphragm above and separated from the stomach wall with great diffi-

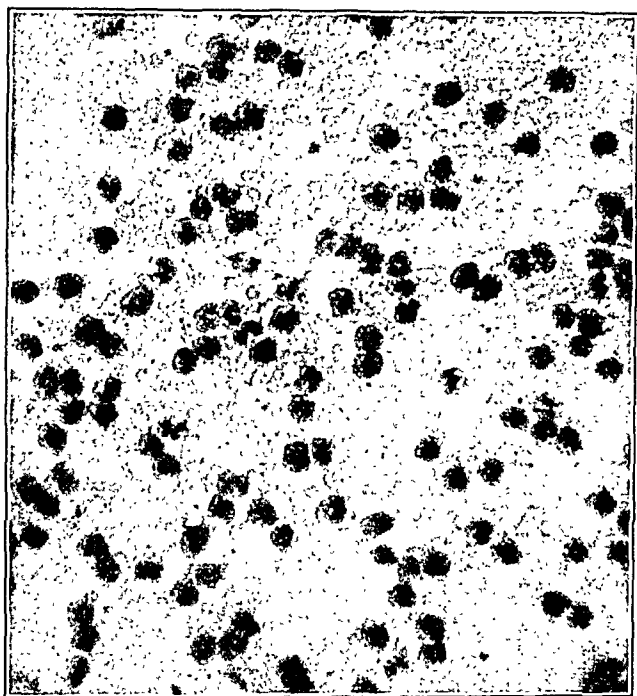


FIG. 1.—Photomicrograph of blood smear, showing the very large number of leukocytes in proportion to the red blood cells.



FIG. 2.—Photomicrograph with higher magnification, showing very well the nuclear structure and giving a suggestive outline of the granules.

culty. Sutures had to be placed in the outer wall of the stomach to close a possible defect. A decided perisplenitis accounted for these adhesions, particularly above and behind. The operation resulted in considerable shock so intravenous saline and other methods of stimulation were resorted to. After the second day recovery was uneventful except for some slight wound drainage, beginning after the sixth day and lasting for a week."

A decided increase in the leukocytes followed almost immediately after the operation. On December 6, 1917, the count was 240,000; on December 8 it was 175,000. This increase of about sixfold, while large, is not so greatly out of proportion as might



FIG. 3.—Photomicrograph with still higher magnifications and beautifully showing the adult type of well-formed nuclei and also showing granules.

appear, since splenectomy or even hysterectomy has been known to transiently increase a low count to a similar degree. The count on December 12 was 50,000; at the time of leaving the hospital, December 29, the count was 45,000. She was able to walk around easily, had lost much of her nervousness and was eating well.

She went away some distance to her home. We had no opportunity for further blood counts, but her daughter reported, from time to time, a rapid improvement in her health, increase in strength, and that she had again assumed her usual household duties.

When she was again seen it was by one of my associates, and at a time when we were having the epidemic of streptococcus lung infection that occurred in the spring of 1918. She entered the

hospital on April 27, 1918, in a comatose condition. She had then been sick about one week. Massive dulness was reported over the bases of both lungs, more on the left than on the right. She was raising bloody, frothy material and died within two hours. An autopsy was not permitted and her sudden death made procrastination in getting blood smears particularly unfortunate.

**Discussion.** The data in this case are lacking in many points of interest. The persistent increase, however, in adult polymorphonuclear leukocytes, associated with splenomegaly was so definite as to merit an analysis of the factors concerned. It requires courage to plunge into any discussion involving the spleen; in so doing we are easily led into a consideration of controversial matter. However, certain light seems to be thrown on the spleen function in the presence of hyperactivity in the bone-marrow yielding an excessive number of leukocytes (even though of normal forms) in the circulating blood.

In the embryo, up to the fourth month of fetal life, both the spleen and bone-marrow form red blood cells; both, together with certain lymph gland and lymph-adenoid tissue, possibly also the liver, form myeloblasts. After the fourth month of fetal life both erythroblasts and myeloblasts are formed almost entirely in the bone-marrow. Thereafter, physiologically and pathologically, we may state that the bone-marrow and the spleen, *in the process of blood regeneration and destruction, work coördinately.*

The normal disposition of incapacitated red blood cells seems to be accomplished largely through the filtration or sieve-like action of the spleen pulp, the discarded material being carted to the liver and becoming the ultimate source of pigment in the bile. Obsolete polymorphonuclear leukocytes seem to meet a similar fate, although probably a large number, particularly when called forth by localized inflammation or other chemotactic influences, are cast off from the body in the form of discharges, such as is seen in purulent sputum, discharging abscess or in pyelocystitis producing pyuria. But when we know that the bone-marrow is hyperfunctioning for considerable periods of time without known avenues of escape for either the excess of red or white cells it seems logical to assume there will be an overfunction of the spleen, with enlargement. Incidentally, we may remark that much more is known concerning the general method of erythrocyte destruction and replacement than of the similar process obtaining for leukocytes.

A consideration of certain well-known pathological entities illustrates well the position taken by the spleen and further demonstrates its response to varying degrees of activity in the bone-marrow. This must be considered for the time being totally regardless of the ultimate etiological factors controlling hematopoietic function:

1. We do not find spleen enlargement in the presence of a severe secondary anemia, for example, that caused by carcinoma of the stomach, with gradual enteric bleeding.

2. In the severest types of fulminating pernicious anemia (aplastic), with fatigued, overtaxed and hypoplastic bone-marrow, we have no spleen or liver enlargement.

3. It is difficult with our present knowledge to speak dogmatically concerning the constancy of spleen hyperfunction in so-called idiopathic pernicious anemia. However, with the H-I index,<sup>1</sup> over one and higher, as elicited by a determination of pigment values in the duodenal contents, and with a patient showing an icteric tendency, spleen enlargement is usually demonstrable.

4. In Vaquez's disease splenomegaly is one of the triad of symptoms upon which the diagnosis is made; the liver is choked with blood-derived pigment.

5. In the anemia of hemolytic icterus, whether familial or acquired, the results of hyperactivity in the bone-marrow are lost through the hyperfunctioning of the enlarged spleen; dramatically enough the disease is cured by splenectomy. This is true whether the inherent stimulus to overdestruction resides in the spleen itself or whether that organ is the unwitting agent of some extraneous factor.

6. The same principle holds with that group of anemias loosely classified as "splenic anemia." When localized spleen disease, notably syphilis or tuberculosis, has been proved, persistent and extreme secondary anemias have been promptly ameliorated by splenectomy.

The inference is left by W. J. Mayo, in an excellent article developing the surgical indications for splenectomy,<sup>2</sup> that the remaining anemias in this group, however named, represent similar splenic processes as yet unknown and unidentified. The abdominal conditions associated with cirrhosis of the liver are similarly given plausible consideration and the splenic factor in visceral circulation analyzed.

7. There is a conversational opinion expressed occasionally by men of experience that myeloid leukemia or myelocythemia represents a malignant overproduction of the bone-marrow, resulting in primitive cell forms, sarcomatous in nature, flooding the circulation. It is true that when this disease is well developed the whole hematopoietic system is involved. Then it is that leukemic tumors may be found in almost any tissue, definitely metastasizing. The much enlarged spleen led to the earlier conclusion that these metastatic agglomerations therein became the source of many of the forms in the blood. The early course of the disease, nevertheless, points strikingly to the attempt on the part of the spleen to exercise the basic function of the pulp spaces to keep these abnormal elements out of the blood, for the same reason as they engulf the broken-down and damaged erythrocytes in malaria. Hence it is that the Mal-

<sup>1</sup> Schneider, J. P.: Further Quantitative Study of Duodenal Blood-derived Pigments, *Arch. Int. Med.*, 1917.

<sup>2</sup> Mayo, W. J.: *Ann. Surg.*, July, 1910.

pighian corpuscles are pushed aside and the pulp spaces become clogged with masses of myeloblastic elements. As further supporting this screen function of the spleen we have:

(a) In the few cases of myeloid leukemia in which splenectomy has been performed the accessory spleens and lymph gland tissues have undergone hyperplasia.

(b) In following the direct vascular connection between the spleen pulp and the liver (well illustrated by pigment deposition in the liver in active pernicious anemia) we see the reason for the earliest, exquisite evidence of invasion of the general tissues in myeloid leukemia (just as in lymph-gland enlargement in the drainage area of the breast in carcinoma the glands withstand the brunt of the invasion, until they are overwhelmed).

There is, therefore, striking argument in support of the general assumption that the spleen exercises physically and pathologically a filtering or screen capacity. At operation in this case there was no indication of liver involvement or glandular enlargement; in other words, nothing to indicate that the spleen was overrun or overpowered. This case, even more than Giffin's, would seem to indicate that under certain conditions there can be a calling forth of particular types of leukocytes, normal in form and structure, without any apparent tendency to ultimate failure on the part of the bone-marrow (as shown by a mobilization of embryonal or immature forms), seeming to exemplify the ability of the bone-marrow to hyperfunction in a benign way. What the chemotactic irritant was in this case must remain unsolved. Splenomegaly, as might be expected, took place to a marked degree. It appears more likely that the massive adhesions about the spleen were the result of hyperactivity and congestion in that organ, with overgrowth of connective tissue rather than the inherent cause of the leukocytosis itself. The long-continued irritation due to the wearing of the pessary is only one possibility and the usual possibilities of focal infection come to mind. Indeed, the ultimate mechanism or device which stimulates or restrains the bone-marrow in its degrees of activity, depending on bodily needs, is poorly understood. It is known that different types of leukocytes appear in the blood under the influence of varying irritants or infections, such as eosinophilia in trichinosis and an increase in large lymphocytes in malaria or pertussis. But wherever this control may be found ultimately to lie it probably follows the rule of other physiological processes: a definite sequence of events transpiring whenever certain elemental stimuli are given recognition. This makes it possible for the ensuing circle of events to be broken in any portion of the chain and the disease picture that results must vary greatly, depending on the position and type of the break. The disturbance of one segment of the hematopoietic system yields lymphatic leukemia or Hodgkin's; overstimulation of the bone-marrow from as yet unknown sources

produces another picture. But whether the end-products of this hyperfunction, circulating in the blood produce the picture of hyperleukocytosis or a leukemia must depend on whether the myeloblastic production is lawful and benign, or Bolshevistic and malignant. In either case splenomegaly can be expected. *The spleen and bone-marrow hyperfunction coördinately.*

For H. Z. Giffin's kindly interest in this case and his opinion and studies of the blood slides as well as the making of the photomicrographs, I wish to acknowledge my deep indebtedness.

### A COMPARATIVE STUDY OF THE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.

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As the result of comparative therapeutic tests conducted by Hata<sup>1</sup> in hen spirillosis and with mice infected with *S. obermayeri*, Ehrlich announced that 0.9 gram neosalvarsan possesses the curative value of 0.6 gram salvarsan; from the practical standpoint of treatment in syphilis this subject is of great importance, and particularly so by reason of the opinions held by several syphilographers of experience that neoarsphenamine in the amounts commonly administered (0.6 to 0.9 gram) does not appear to possess the same therapeutic activity as arsphenamine (0.4 to 0.6 gram).

**Purpose of Investigation.** In our experiments conducted for the purpose of ascertaining the comparative therapeutic activity of arsphenamine and neoarsphenamine, we utilized rats infected with a virulent strain of *T. equiperdum*, to ascertain the smallest amounts of arsphenamine and neoarsphenamine, produced by other laboratories and by ourselves, that would sterilize animals infected twenty-four hours before with intraperitoneal injections of approximately known numbers of trypanosomes. Inasmuch as the trypanosomes in the control animals appeared in the peripheral blood within forty-eight hours and caused death in from the fifth to seventh day, these experiments yielded quite sharp and definite results, although constituting a severe test of the therapeutic activity of the compounds.

A second purpose of these studies was to determine whether differ-

<sup>1</sup> The Experimental Chemotherapy of Spirillosis, Rebman, London, 1911.



ent lots of arspenamine and neoarsphenamine showed variation in their trypanocidal activity, in the same manner that their toxicity is likely to vary;<sup>2</sup> this is likewise a subject of much practical importance from the standpoint of standardization of these compounds.

**Practical Value of Trypanocidal Tests for Determining the Curative Properties of Arspenamine and Neoarsphenamine.** From the standpoint of treatment of syphilis, therapeutic tests employing rabbits infected with *T. pallidum* are in some respects to be preferred, but rabbits vary considerably in susceptibility to testicular and generalized infections, tend to recover spontaneously, the *Treponema* is very susceptible to the influence of arsenical compounds, and is not well adapted for experiments designed to elicit sharp differences in therapeutic activity; furthermore, thorough examinations of the lesions for evidences of therapeutic effects are very laborious and time consuming. In addition very large numbers of rabbits are required for testing a few compounds, adding greatly to the expense and labor involved.

Trypanocidal tests, however, utilize a smaller and cheaper animal, infections are regular and sure, the evidences of therapeutic activity insofar as arspenamine and neoarsphenamine are concerned are sharp and decisive, and not more than two or three weeks of observation are required for the results.

*Insofar as comparative therapeutic tests with arspenamine and neoarsphenamine are concerned we believe that trypanocidal tests may be accepted as an index of therapeutic activity because both compounds are markedly trypanocidal; the value of these tests is, however, sharply limited inasmuch as certain other medicinals of value in the treatment of pallida infections, notably the mercurials,<sup>3</sup> are unable to influence the course of experimental trypanosomiasis, due in part to their high toxicity which thereby prevents the administration of sufficiently large doses; trypanocidal tests may be regarded therefore as possessing a positive value only, that is, they may be taken as a method of determining comparative therapeutic activity of medicinals possessing trypanocidal activity *in vivo*; medicinals such as the mercurials which fail to influence trypanosomiasis of animals, may still possess spirocheticidal properties and for this reason negative trypanocidal tests are of little or no value in excluding the therapeutic activity of these compounds in syphilis.*

We are not aware of any evidence that tends to invalidate the proposition that arspenamine and neoarsphenamine proving trypanocidal *in vivo* will exert spirocheticidal properties *in vivo* and prove therapeutically active in syphilis; as stated above, how-

<sup>2</sup> Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: Comparative Studies of the Toxicity of Arspenamine and Neoarsphenamine, *AM. JOUR. MED. SC.* (To be published later).

<sup>3</sup> Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: The Chemotherapy of Mercurial Compounds, *Am. Jour. Syph.*, 1917, i, 1-43.

ever, the converse is not necessarily true, that is, medicinals as the mercurials, failing to influence trypanosomiasis will not necessarily fail to influence infections with *T. pallidum*.

As stated by Pearce and Brown<sup>4</sup> the treatment of experimental trypanosomiasis of mice and rats is largely a matter of speed of action yielding valuable data in a relatively short space of time on the therapeutic activity of a compound. These investigators, however, have very properly stated that experiments of this character do not involve the treatment of chronic tissue changes as in trypanosomiasis of guinea-pigs and rabbits, which are more nearly analogous to the naturally acquired forms of the disease, but that the two types of infections supplement each other in the chemotherapy of experimental trypanosomiasis.

**Technic of Trypanocidal Tests.** The strain of *T. equiperdum* employed in our experiments appears in the peripheral blood (tail) within forty-eight to seventy-two hours after intraperitoneal infection; by the fifth to seventh days after infections enormous numbers of trypanosomes are in the blood and may outnumber the erythrocytes. The animals usually die on the fifth to seventh days. We have found the results with this strain to be sharper and more decisive than those observed with the relatively non-virulent *T. lewisi* and better than with *T. brucei*, which is usually too virulent and kills too quickly.

Rats weighing from 100 to 150 gm. are employed; pregnant animals are excluded. Each animal is weighed after eighteen hours' fasting and injected with a dose of arspenamine or neoarsphenamine according to body weight. (See Table I.)

The question of infection is very important in relation to the results of these tests; we routinely infect twenty-four hours before administering the medicinal, the infection having this much headway before treatment begins. The number of trypanosomes used in infecting the animals greatly influences the results as shown in a previous paper by Kolmer;<sup>5</sup> infection with a great number of trypanosomes requires a much larger dose of arspenamine or neoarsphenamine for sterilization than infection with a small number, and the method proposed for counting the trypanosomes and infecting with approximately known numbers with blood removed aseptically from the heart of the seed animal<sup>6</sup> has proved of distinct value. It is only by using rats of approximately the same weight and infecting with approximately known numbers of trypanosomes by intraperitoneal injection that the experiments are rendered uniform

<sup>4</sup> Experimental Trypanosomiasis: its Applications in Chemotherapeutic Investigations, Jour. Exper. Med., 1918, xxviii, 109-147.

<sup>5</sup> A Method of Transmitting Known Numbers of Trypanosomes, with a Note on the Numeric Relationship of Trypanosomiasis to Infection, Jour. Infect. Dis., 1915, xvii, 79-94.

<sup>6</sup> Kolmer, J. A.: A Method of Transmitting Blood Parasites, Jour. Infect. Dis., 1915, xvi, 311-312.

TABLE I.—THE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.\*

No.	Wt., gm.	Sex.	Compound.	Dose per kilo.	Results in days after treatment.											
					1	2	3	4	5	6	7	8	9	10	11	12
1	145	F.	Nearsphen. (Lab. No. 2)	0.010	—	—	—	—	—	—	—	Few	+	+	+	+
2	130	M.		0.015	—	—	—	—	—	—	—	—	Few	+	+	+
3	150	F.		0.020	—	—	—	—	—	—	—	—	—	—	—	—
4	160	F.		0.030	—	—	—	—	—	—	—	—	—	—	—	—
5	140	M.		0.040	—	—	—	—	—	—	—	—	—	—	—	—
6	145	F.	Nearsphen. (Lab. No. 2)	0.010	—	—	Few	+	+	+	+	D.	+	+	+	+
7	160	F.		0.015	—	—	—	—	—	Few	+	+	+	+	+	+
8	130	M.		0.020	—	—	—	—	—	—	+	+	+	+	+	+
9	170	M.		0.030	—	—	—	—	—	—	+	+	+	+	+	+
10	170	F.		0.040	—	—	—	—	—	—	—	—	—	+	+	+
11	145	F.	Arsphen. (Lab. No. 2)	0.005	—	—	—	—	—	—	—	Few	+	+	+	+
12	115	F.		0.008	—	—	—	—	—	—	—	Few	+	+	+	+
13	210	M.		0.010	—	—	—	—	—	—	—	—	—	+	+	+
14	180	F.		0.015	—	—	—	—	—	—	—	—	—	+	+	+
15	150	F.		0.020	—	—	—	—	—	—	—	—	—	+	+	+
16	170	M.	Controls	0	—	Few	+	+	+	+	D.	—	—	—	—	—
17	165	F.		0	—	Few	+	+	+	+	D.	—	—	—	—	—
18	215	M.		0	—	Few	+	+	+	+	D.	—	—	—	—	—
19	140	F.		0	—	—	Few	+	+	+	+	—	—	—	—	—

\* Rats infected twenty-four hours previously with intraperitoneal injections of 231,000 T. equiperdum.

† This rat developed trypanosomiasis on the sixteenth day and died on the nineteenth day.

and comparative;<sup>7</sup> additional experiments by Kolmer and Yagel<sup>8</sup> have emphasized the importance of these factors in the technic, and have shown that when the animals vary greatly in weight, best results are secured by infecting with trypanosomes according to the weight of each animal. With rats weighing from 100 to 200 gm. uniform infections are secured with 250,000 to 500,000 trypanosomes per rat; lighter infections suffice and render the results more delicate as shown in Table II, but under these conditions one or more of the controls may not develop trypanosomiasis and thereby cloud the interpretation of the entire experiment.

TABLE II.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.\*

Compound.	Dose per kilo.	Results in days after treatment.						
		1	2	3	4	5	6	7
Arsphenamine (Lab. No. 2)	0.008	—	—	—	—	—	—	—
	0.010	—	—	—	—	—	—	—
	0.020	—	—	—	—	—	—	—
	0.030	—	—	—	—	—	—	—
Neoarsphenamine (Lab. No. 2)	0.010	—	—	—	—	—	—	—
	0.020	—	—	—	—	—	—	—
	0.030	—	—	—	—	—	—	—
	0.040	—	—	—	—	—	—	—
Neoarsphenamine (Lab. No. 2)	0.010	—	—	—	Few	+	++++	D.
	0.020	—	—	—	—	—	Few	++++
	0.030	—	—	—	—	—	—	—
	0.040	—	—	—	—	—	—	—
Neoarsphenamine (Lab. No. 2)	0.010	—	—	—	Few	+	++++	D.
	0.020	—	—	—	—	—	Few	++++
	0.030	—	—	—	—	—	—	—
	0.040	—	—	—	—	—	—	—
Controls . . .	None	—	—	—	Few	+	+++	D.
	None	—	—	—	Few	+	++++	D.

\* Rats infected with 180,000 *T. equiperdum*.

The dose of arsphenamine and neoarsphenamine is prepared separately for each rat in small sterile vials and is contained in 1 c.c. which is slowly injected with a syringe in a saphenous vein; in testing arsphenamine doses ranging from 0.005 to 0.020 gm. per kilogram of rat were generally administered and neoarsphenamine in doses ranging from 0.008 to 0.040 gm. per kilo.

The blood of each animal, including the controls, is examined each day over a period of three weeks by placing a drop from the tail on a cover-glass and allowing the blood to spread in a film when placed upon a slide; the results are recorded numerically as few,

<sup>7</sup> Kolmer, J. A., Schamberg, J. F., and Raiziss, G. W.: The Numeric Relationship of Infection to the Chemotherapy of Experimental Trypanosomiasis, Jour. Infect. Dis., 1917, xx, 35-44.

<sup>8</sup> A Further Study of the Numerical Relationship of Infection to Experimental Trypanosomiasis and Influence upon Chemotherapeutic Tests. (To be published.)

TABLE III.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.\*

Compound.	Dose per kilo.	Results in days after treatment.							
		1	2	3	4	5	6	7	8
Neorsphenamine (Lab. No. 2)	0.010	....	....	+	++	++	D.	-	-
	0.020	-	-	-	-	-	-	-	-
	0.030	-	-	-	-	-	-	-	-
	0.040	-	-	-	-	-	-	-	-
Neorsphenamine (Lab. No. 5)	0.010	-	+	++	++	D.	-	Few	+
	0.020	-	-	-	-	-	-	-	-
	0.030	-	-	-	-	-	-	-	-
	0.040	-	-	-	-	-	-	-	-
Neorsphenamine (Lab. No. 3)	0.010	....	....	....	....	....	Few	++	+
	0.020	-	-	-	-	-	-	-	-
	0.030	-	-	-	-	-	-	-	-
	0.040	-	-	-	-	-	-	-	-
Neorsphenamine (Lab. No. 6)	0.010	-	-	-	-	-	-	+	+
	0.020	-	-	-	-	-	-	-	-
	0.030	-	-	-	-	-	-	-	-
	0.040	-	-	-	-	-	-	-	-
Neorsphenamine (Lab. No. 2)	0.010	-	-	-	-	-	-	-	-
	0.020	-	-	-	-	-	+	D.	-
	0.030	-	-	-	-	+	+	+	+
	0.040	-	-	-	-	-	Few	-	-
Arsphenamine (Lab. No. 1)	0.008	-	-	-	+	-	-	-	-
	0.010	-	-	-	-	-	-	-	-
	0.020	-	-	-	-	+	+	-	+
	0.030	-	-	-	-	-	-	-	-
Controls	None	Few	++	++	++	D.	-	-	-
	None	Few	++	++	++	D.	-	-	-

\* Rats infected with 500,000 T. equiperdum.

† These rats developed trypanosomiasis after the eighth day and died about five days later.

+, ++, +++ and +++++, the latter referring to the presence of numbers of trypanosomes too numerous to be counted.

TABLE IV.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.\*

Compound.	Dose per kilo.	Results in days after treatment.						
		1	2	3	4	5	6	7
Arsphenamine (Lab. No. 2)	0.008	—	+	++++	D.	—	—	—
	0.010	—	—	—	—	—	—	—
	0.020	—	—	—	—	—	—	—
	0.030	—	—	—	—	—	—	—
Neoarsphenamine (Lab. No. 2)	0.010	Few	+	++++	D.	—	—	—
	0.020	—	—	—	—	—	—	—
	0.030	—	—	—	—	—	—	—
	0.040	—	—	—	—	—	—	—
Neoarsphenamine (Lab. No. 4)	0.010	Few	++	++++	D.	—	—	—
	0.020	—	Few	++++	D.	—	—	—
	0.030	—	—	—	—	—	—	—
	0.040	—	—	—	—	—	—	—
Controls . . .	None	Few	++++	++++	D.	—	—	—
	None	—	+	++++	++++	D.	—	—
	None	Few	++++	++++	D.	—	—	—
	None	—	+	++++	++++	D.	—	—

\* Rats infected with 600,000 T. equiperdum.

† This rat developed trypanosomiasis on eighth day and died on twelfth day.

TABLE V.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.\*

Compound.	Dose per kilo.	Results in days after treatment.						
		1	2	3	4	5	6	7
Arsphen. (Lab. No. 2)	0.030	—	—	—	—	—	—	—
	0.020	—	—	—	—	—	—	—
	0.010	—	—	—	—	—	+	+++
	0.008	—	—	—	Few	+	+++	D.
	0.005	—	—	—	—	D.	—	—
	0.003	—	Few	+	++	+++	++++	D.
Neoarsphen. (Lab. No. 2)	0.040	—	—	—	—	—	—	—
	0.030	—	—	—	—	—	—	—
	0.020	—	—	—	—	—	—	—
	0.010	—	—	—	+	++++	++++	D.
	0.008	—	—	+	++	++++	D.	—
	0.005	—	Few	++++	D.	—	—	—
Controls . . .	None	+	++++	D.	—	—	—	—
	None	Few	++++	++++	D.	—	—	—
	None	Few	+++	++++	++++	D.	—	—
	None	+	+++	++++	++++	D.	—	—

\* Rats infected with 500,000 T. equiperdum.

† Developed trypanosomiasis on eighth day; died on fourteenth day.

A twenty-one-day period of observation is necessary, inasmuch as trypanosomes may appear in the peripheral blood of animals

TABLE VI.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.\*

Compound.	Dose per kilo.	Results in days after treatment.							
		1	2	3	4	5	6	7	8
Nearsphenamine (Lab. No. 2)	0.008	—	—	—	—	Few	++	++	D.
	0.008	—	—	—	+	++	++	D.	D.
	0.010	—	—	—	Few	+	++	++	++
	0.010	—	—	—	Few	+	++	++	+
	0.020	—	—	—	—	—	—	—	Few
	0.020	—	—	—	—	—	—	—	†
	0.030	—	—	—	—	—	—	—	—
Arsphenamine (Lab. No. 2)	0.003	—	Few	+	++	++	++	D.	D.
	0.003	—	Few	+	++	++	D.	++	++
	0.008	—	—	—	Few	+	++	+	D.
	0.008	—	—	—	Few	+	++	+	++
	0.010	—	—	—	—	—	Few	+	++
	0.010	—	—	—	—	—	+	+	+
	0.020	—	—	—	—	—	—	—	—
Controls	None	Few	++	++	D.	D.	—	—	—
	None	Few	++	++	++	—	—	—	—

\* Rats infected with 500,000 T. equiperdum.

† Rat developed trypanosomiasis on the eleventh day and died on the fourteenth.

treated with arspenamine and neoarsphenamine as late as sixteen days after infection; all rats proving sterile at the end of three weeks usually live indefinitely insofar as the effects of the experiment are concerned. The examination for trypanosomes in the tail blood begins on the day following treatment which is the third day after infection; the results are recorded in this manner. (See Tables I to VI.) As is usual in tests of this kind the results are never mathematically accurate and rats frequently die without showing trypanosomes in their blood.

TABLE VII.—THE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE PREPARED BY DIFFERENT LABORATORIES.

Compounds.	Smallest sterilizing doses per kilogram of weight.									Average.
	Exper. 1.	Exper. 2.	Exper. 3.	Exper. 4.	Exper. 5.	Exper. 6.	Exper. 7.	Exper. 8.	Exper. 9.	
Lab. No. 1 . .	0.02	0.02	..	..	..	..	..	..	..	0.0200
Lab. No. 2 . .	0.02	0.03	0.02	0.02	0.02	0.01	0.015	0.02	0.015	0.0188
Lab. No. 3 . .	0.03	0.02	..	..	..	..	..	..	..	0.0250
Lab. No. 4 . .	0.03	0.03	0.02	..	..	..	..	..	..	0.0260
Lab. No. 5 . .	0.02	0.03	0.02	..	..	..	..	..	..	0.0230
Lab. No. 6 . .	0.02	0.03	..	..	..	..	..	..	..	0.0250

TABLE VIII.—THE TRYPANOCIDAL ACTIVITY OF NEOARSPHENAMINE PREPARED BY DIFFERENT LABORATORIES.

Compounds.	Smallest sterilizing doses per kilogram of weight.							Average.
	Exper. 1.	Exper. 2.	Exper. 3.	Exper. 4.	Exper. 5.	Exper. 6.	Exper. 7.	
Lab. No. 1 . . . .	0.04	0.02	More than 0.04	0.03	..	..	..	0.043 +
Lab. No. 2 . . . .	0.04	0.03	0.03	0.04	More than 0.04	0.02	0.03	0.033 +
Lab. No. 3 . . . .	0.03	0.02	More than 0.04	..	..	..	..	0.030 +
Lab. No. 4 . . . .	0.04	0.04	..	..	..	..	..	0.040 +
Lab. No. 5 . . . .	0.03	0.02	0.04	0.04	..	..	..	0.033 +
Lab. No. 6 . . . .	0.04	0.04	..	..	..	..	..	0.040

**Results.** The results of a number of experiments with arspenamine and neoarsphenamine prepared by six different laboratories are shown in Tables I to VI as examples; a summary of these tests



is presented in Tables VII and VIII giving the smallest amounts of each compound per kilogram of rat, proving sufficient for sterilization of the animal, as determined by a period of three weeks of observation.

**Summary.** 1. The smallest trypanocidal doses of arsphenamine (for the strain used in our experiments) ranged from 0.010 to 0.030 gm. per kilogram of body weight of rat; the average for the arsphenamines of the six different laboratories ranged from 0.0188 to 0.026 gm. per kilogram of weight, giving a general average based upon tests conducted with twenty-one compounds, of about 0.023 gm. per kilogram of weight as the trypanocidal dose.

2. The smallest trypanocidal doses of neoarsphenamine ranged from 0.020 to more than 0.040 gm. per kilogram of body weight; the average for the neoarsphenamines of the six different laboratories ranged from 0.030 to more than 0.043 gm. per kilogram of rat, giving a general average based upon tests conducted with twenty-two compounds, of from 0.037 to 0.040 gm. per kilogram of weight, as the trypanocidal dose.

3. According to these tests arsphenamine is about 1.7 times as trypanocidal as neoarsphenamine, the ratio being:

$$\frac{\text{Smallest trypanocidal dose of arsphenamine, 0.023 gram}}{\text{Smallest trypanocidal dose of neoarsphenamine, 0.04 gram}} = 1.74$$

According to Castelli's<sup>9 10</sup> report (see Table IX) the following ratios may be made out for other microparasites:

$$\frac{\text{Smallest dose of arsphenamine for S. obermayer, 0.10656 gram}}{\text{Smallest dose of neoarsphenamine for S. obermayer, 0.1998 gram}} = 1.78$$

$$\frac{\text{Smallest dose of arsphenamine for hen spirillosis, 0.0035 gram}}{\text{Smallest dose of neoarsphenamine for hen spirillosis, 0.006 gram}} = 1.7$$

$$\frac{\text{Smallest dose of arsphenamine for rabbit syphilis, 0.0235 gram}}{\text{Smallest dose of neoarsphenamine for rabbit syphilis, 0.035 gram}} = 1.5$$

TABLE IX.—THERAPEUTIC DOSES OF SALVARSAN AND NEOSALVARSAN AS GIVEN BY CASTELLI.

Animal.	Infection.	Route of administration.	Sterilizing doses per kilo.	
			Salvarsan.	Neosalvarsan.
Mouse . . .	Recurrent fever	Subcutaneous	0.10656	0.1665
	Recurrent fever	Intravenous	0.10656	0.1998
Hen . . . .	Spirillosis	Intramuscular	0.00350	0.0060
Rabbit . . .	Syphilis	Intravenous	0.02-0.027	0.03-0.04*

\* Doses killing spirochetes in testicular lesions in twenty-four hours.

<sup>9</sup> Castelli, G.: Ueber Neosalvarsan. Bestimmung der Toxizität und der heilenden Wirkung bei experimentellen Spirochätenkrankheiten, Ztschr. f. chemotherapie orig., 1912-1913, i, 321-352.

<sup>10</sup> Castelli, G.: Ueber Neosalvarsan, Ztschr. f. chemotherapie, orig., 1912-1913, i, 122-135.

Our results are therefore in close agreement with those of Castelli and indicate that arspfenamine is from 1.5 to almost 1.8 times more active therapeutically against virulent trypanosomes, spirilla and *T. pallida* than neoarsphenamine; it is also of interest to note in this connection the close parallelism among the ratios for the different microparasites employed in these tests by Castelli and ourselves.

4. According to these results Ehrlich's ratio of therapeutic activity given as 0.6 gm. arspfenamine equal to 0.9 gm. neoarsphenamine is incorrect; rather 0.6 gm. arspfenamine is equal to about 1.05 gm. neoarsphenamine. In the treatment of syphilis with neoarsphenamine either larger doses are indicated than are usually given or probably better still, the same or smaller doses at more frequent intervals.

5. The ratio of *dosis therapeutica* to *dosis tolerata* of the two compounds is very interesting and may be stated as follows:

(a) The trypanocidal dose (*dosis therapeutica*) of arspfenamine is 4.56 times less the highest tolerated dose (*dosis tolerata*) according to the ratio:

$$\frac{\text{Dosis tolerata, 0.105 gram per kilo}}{\text{Dosis therapeutica, 0.023 gram per kilo}} = 4.56$$

(b) The trypanocidal dose of neoarsphenamine is 6.35 times less the highest tolerated dose according to the ratio:

$$\frac{\text{Dosis tolerata, 0.254 gram per kilo}}{\text{Dosis therapeutica, 0.04 gram per kilo}} = 6.35$$

From these results it is evident that neoarsphenamine is a safer drug; even when doses of 1 gm. of neoarsphenamine which approximates 0.6 gm. of arspfenamine in therapeutic activity are given in the treatment of syphilis there remains a larger margin of safety.

**Conclusions.** 1. Trypanocidal tests employing rats infected with *T. equiperdum* provide a means for determining the curative properties of arspfenamine and neoarsphenamine.

2. Such medicinals as arspfenamine and neoarsphenamine proving trypanocidal *in vivo* are probably curative in syphilis; other compounds as the mercurials, which are unable to influence experimental trypanosomiasis, may still influence infections with *T. pallida*; trypanocidal tests possess, therefore, a greater positive than negative value in chemotherapeutic studies in syphilis.

3. In conducting trypanocidal tests the virulence of the strain, the method of infection, the interval between infection and treatment and the weight of the test animals are modifying factors and must be rendered uniform to secure satisfactory results.

4. With the strain of *T. equiperdum* employed in these experiments the smallest amounts of arspfenamine sterilizing rats infected

twenty-four hours previously varied from 0.010 to 0.030 gm. per kilo of body weight, the general average for twenty-one compounds prepared by six different laboratories, being 0.023 gm. per kilo of rat.

5. The smallest sterilizing doses of neoarsphenamine under identical conditions varied from 0.020 gm. to more than 0.040 gm. per kilo of rat; the general average for twenty-two compounds from six different laboratories was about 0.040 gm. per kilo.

6. The trypanocidal activity of different lots of arsphenamine and neoarsphenamine prepared by the same laboratory and by different laboratories varied in a manner analogous to variations in lethal toxicity for rats.

7. The trypanocidal activity of arsphenamine is 1.74 times greater than that of neoarsphenamine; in experimental infections with *S. obermayeri*, hen spirillosis and rabbit syphilis, Castelli found arsphenamine from 1.5 to 1.78 times more active therapeutically than neoarsphenamine.

8. According to these results 0.6 gm. arsphenamine equals 1.05 rather than 0.9 gm. of neoarsphenamine in therapeutic activity.

9. The trypanocidal dose (*dosis therapeutica*) of arsphenamine is 4.56 times less the highest tolerated dose for the rat (*dosis tolerata*); the trypanocidal dose of neoarsphenamine is 6.35 times less the highest tolerated dose.

10. These results indicate that neoarsphenamine is a somewhat safer compound than arsphenamine; even when 1 gm. of neoarsphenamine is administered as equivalent in therapeutic activity to 0.6 gm. arsphenamine, the margin of safety is greater.

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## CONTRACTION WAVES IN THE NORMAL AND HYDRONEPHROTIC URETER: AN EXPERIMENTAL STUDY.

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MOST of the extensive work that has been done on hydronephrosis has been confined to the kidneys. At the suggestion of Dr. W. C. Quinby the experiments reported here were undertaken to study the ureter in this condition.

METHOD. Rabbits were found to lend themselves readily to observation of the ureter *in situ*, while dogs were used both for this purpose and for the study of ureteral peristalsis *in vitro*. The method employed was briefly as follows:

Each animal was etherized. With strict aseptic precautions a small ventral incision was made in the abdomen and a rubber band of small caliber fastened about one ureter, just above the bladder, so as to cause a partial constriction. In a few cases this ligation was made higher up. The abdominal incision was then closed.

An incomplete ligation was preferred to a complete one for the following reasons: (a) The resultant hydronephrosis is of slower development but greater in degree.<sup>1 2</sup> (b) The condition would thus more nearly resemble clinical hydronephrosis which is usually caused by partial or recurring obstruction. (c) Only in one recorded experimental case has atrophy of the kidney followed incomplete ligation, whereas it almost always follows complete ligation.<sup>3</sup>

After a period varying from three weeks to five months a second operation was performed. The dogs were etherized a second time, the rabbits were anesthetized with paraldehyde. A long, ventral abdominal incision was now made, the rectum cut across at its lowest point and all of the intestines reflected upward after cutting the root of the mesentery as high as the superior mesenteric artery. This exposed both ureters to inspection throughout their course. The whole preparation was placed for observation under glass in a chamber maintained at a temperature of 38° C.

After observation *in vivo*, both the normal and hydronephrotic ureters were removed from the dog and placed in oxygenated Locke's solution\* at 38° C. During the succeeding twelve hours experiments were performed on each ureter. Instead of excising separate strip or ring segments, as previous experimenters have done,<sup>4 5 6 7 8</sup> the whole ureter was preserved intact. A ring segment of about 1 cm. at either end of the ureter was caused to record its contractions by means of loops of fine silk passed on a needle† through the ureter wall and out at the end of the ureter. Thus a ring of circular muscle was included in the loops. These segments were connected in this way with light, balanced, writing levers which registered on a smoked drum. The beginning and the end of a wave of peristalsis, or retroperistalsis, was thus graphically recorded as well as the time required for the passage of the wave.

As a result of the first operation marked unilateral dilatation of the ureter and pelvis was found in every case but one, a series of thirty-two animals being used. In previous experiments on hydronephrosis atrophy of the ureter walls has been found in the great majority of cases.<sup>9 10</sup> This may have been due to the fact that *complete* ligation has been employed by most observers. In the experiments reported here the wall of the dilated ureter was found to be much hypertrophied in the majority of instances and microscopic

\* For the most satisfactory composition of Locke's solution, see note 7.

† It was found necessary to use the finest needles and silk such as are employed in suturing bloodvessels. The needles were blunted a little to ensure against injury to the wall of the ureter after passing through it.

examination showed that this occurred in all three muscle layers. In three experiments the rubber bands cut quite through the wall of the ureter. In two of these cases the ureter had reestablished its lumen and apparently functioned as before ligation. Two of the

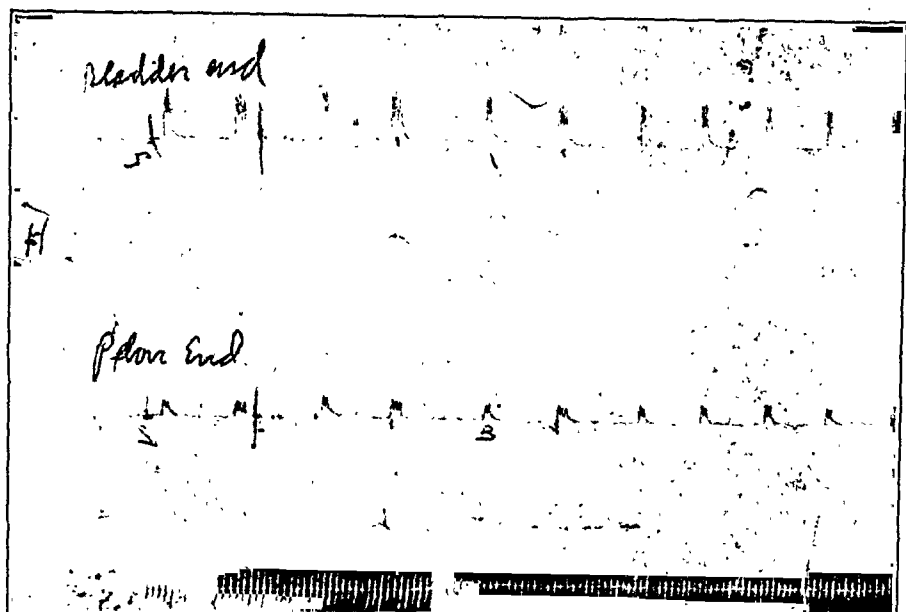


FIG. 1.—Dog 128, June 25. Normal ureter in Locke's solution. The peristaltic waves were complete. The bladder end of the ureter acted as pacemaker throughout the experiment; time marked in five-second intervals.

rubber bands were found free inside the hydronephrotic sac. Caulk and Fisher<sup>10</sup> have shown that the lumen may be restored after complete ligation by epithelial outgrowths of the wall from above and below the ligation in six weeks' time.

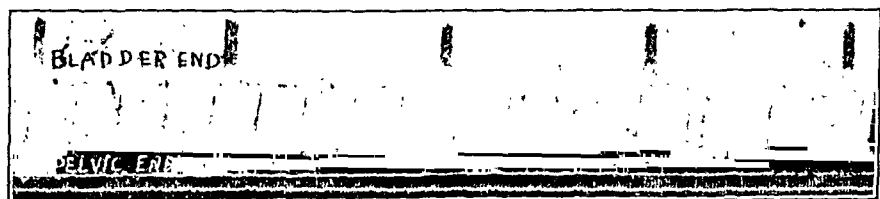


FIG. 2.—Normal ureter excised from a dog that had had no previous operation. The ring segments contracted independently throughout the experiment. This form of curve with groups of rapid contraction separated by long intervals of rest was exhibited by the bladder end of the ureter in several experiments.

In each case where there had been no interference with the ureter the direction of peristalsis was from renal pelvis to bladder, even when the ureter was dilated to over 1 cm. in diameter. In such cases the pressure throughout must have been the same. This would show that the stimulus of the pressure of freshly secreted

urine in the pelvis is not necessary to inaugurate peristaltic waves at this point.

When the ureters were excised and suspended in oxygenated Locke's solution as described above the origin of spontaneous peristaltic waves varied. This was true of both the normal and dilated ureters. Waves were as likely to pass up as down the ureter or even to alternate. In six cases it happened that few or no complete peristaltic waves occurred. Instead the segments at the two ends contracted independently. In three of these latter experiments the rate of contraction of the segment at the pelvic end was faster than that at the other end. In the other three experiments the rates at the two ends were about the same. No consistent difference in the conformation of the curve made by the contraction of rings at different levels was noted, as mentioned by Satani when working with pigs' ureters.

Observations were made on the action of a few of the more important drugs on the excised ureter, but no exhaustive study of the pharmacology of the ureter was undertaken.\*

It has been observed by numerous experimenters that antiperistalsis may be induced by mechanical stimulus applied directly to the ureter. Levin and Goldschmidt<sup>14</sup> in 1893 caused a passage of colored solution from the bladder to the pelvis of the kidney by mechanical stimulation of the bladder. No reference to a repetition of these experiments was found in the literature of the ureter. In 1911 Cannon<sup>15</sup> showed the possibility of inducing antiperistalsis in the colon. He observed the formation of a local constriction ring following stimulation mechanically or with barium chloride, and that this ring beat rhythmically, thus inaugurating simultaneous waves of peristalsis and antiperistalsis. Up to this time nothing analogous to this has been demonstrated in the ureter.

In experiment 10 the abdomen was opened, the intestines reflected upward and the rabbit placed in a warm box as usual. The dilated ureter was pinched between forceps. A ring of con-

\* In view of the recent stimulating work on the pharmacology of the ureter by Macht,<sup>11 12 13</sup> and still more recently by Satani,<sup>8</sup> it may be of interest to note the effect of a few drugs on the whole excised ureter of a dog, as distinguished from the separate ring segments of pig ureters used by the two above-mentioned experimenters. In both normal and hypertrophied ureters epinephrin produced an increased rate of contraction. No effect on the conductivity was detected and the two ends responded equally. 0.015 gm. papaverin in 50 c.c. Locke's solution decreased the tone of the ureter and the rate and amplitude of contraction. The bladder end, in fact, was quickly paralyzed while the pelvic end continued at a slower rate. Nicotin caused a marked increase in the tonus and rate of contraction at both ends, which was followed by paralysis. Pilocarpin and atropin were added to Locke's solution in four cases. In three there was no effect. In the fourth, after the addition of 0.13 gm. pilocarpin to 50 c.c. Locke's solution, there was a small but definite increase in the rate of both the pelvic and bladder segments. This was followed by 0.013 gm. atropin, which made the contraction rate a little slower. In these experiments these two last drugs had very slight effect on the ureter, if any, and one would be led to suppose that in therapeutic doses they would have no effect.

traction formed at once and in a few seconds a single contraction wave was sent out simultaneously in each direction. After this, however, the area acted as a block, arresting the spontaneous waves of peristalsis from above and thus permitting the lower half of the ureter to contract independently. At a rate much slower than the previous normal peristalsis, waves of retroperistalsis passed from a point in the ureter just above the bladder upward to the block. This continued for about fifteen minutes. During this time the traumatised area acted like a Stannius ligature on the heart, cutting off stimuli from the normal pacemaker in the pelvis or pelvi-ureteral junction.

In experiment 14, performed on a rabbit, it was found that the application of a drop of dilute solution of barium chloride to the dilated ureter *in situ*, resulted in the production of a local ring of tonic constriction. From this point, at intervals of about twenty seconds, waves of contraction were sent off simultaneously in both directions. This area of increased tonus could not be seen to beat, as could the rings in the colon described by Cannon, but otherwise the phenomena are quite similar. It is probable that if the ureter were larger the ring would be seen to beat with the inauguration of each contraction wave. Later, normal waves of peristalsis originating at the pelvis recurred and the antiperistalsis ceased. Moderate pressure upon this hydro-ureter showed that urine could be forced out through the constricting rubber band. In experiment 27, this time on a dog, the occlusion of the lumen of the dilated ureter was functionally complete, as no urine was seen to emerge from the ureteric orifice into the bladder following peristaltic waves. On this ureter the above experiment was repeated with a similar result, waves passing outward in both directions from the ring of increased tonus every four seconds.

DISCUSSION. In the last two experiments above cited the constriction ring became pacemaker and controlled the whole ureter, in virtue of the fact that its rhythm was more rapid than the rhythm of spontaneous contraction in any other part of the ureter or pelvis. The rate of discharge from the rings in the two cases was twenty and four seconds respectively. When the irritability of these areas had become less the rhythm became slower and the pelvis returned to its role of inaugurating peristalsis.

In those cases in which the proximal and distal rings beat independently in Locke's solution the rate of the kidney ring was more rapid than that of the bladder ring in a rather small majority of cases. But in those cases in which spontaneous peristalsis was complete *in vitro* the location of the pacemaker was found to be in one end as frequently as in the other. Satani found that the single excised segments of ureter from the pelvic end beat more rapidly in Locke's solution than segments from the other end. Boulet and Gley<sup>16</sup> observed that the upper segment of a human

ureter contracted more rapidly in Locke's solution than the lower segment. Stern<sup>17</sup> observed normal ureteral peristalsis two weeks after nephrectomy. We may conclude that the rhythmicity of the upper ureter is usually more rapid than that of the lower end, but the fall in rate is not very marked and the difference easily upset. There is an area in the pelvis, however, whose rate of spontaneous contraction is much above that of the ureter. Nagel<sup>18</sup> noted that after making a section at the pelvi-ureteral junction the pelvis continued to contract without interruption. In some of the present experiments, in which the ureter was distended to the most extreme degree, it was noted on opening the abdomen that the contraction caused by the peristaltic wave at the upper end of the ureter was so weak as to be scarcely visible, but a shadow-like wave always began at the pelvis and passed downward to the lower ureter where the distention was usually less and the contractions always more vigorous. There is, therefore, an area in the renal pelvis whose spontaneous contraction rate is normally higher than that of any part of the ureter and which acts as pacemaker.

Child<sup>19</sup> has shown that tissues with a rapid rate of oxidation are more susceptible to certain poisons, *e. g.*, KCN, than tissues with a slow rate. He showed in ctenophore that in passing from the aboral to the oral end there is a gradation of susceptibility to the poison and a corresponding gradation in the metabolic activity at the successive levels. He proposed the hypothesis that all axiate organisms, as well as all axiate structures in complex organisms, have a gradient of metabolism underlying their activity. As examples of axiate structures or organs, take the intestine, the Fallopian tubes or the ureter. According to Child, that area will dominate the whole organ which has the highest rate of metabolism. Peristaltic waves will follow a definite gradient of forces passing from an area of high rate of metabolic activity to areas of lower rate. This descending pathway is called the metabolic gradient. Hyman<sup>20</sup> showed that regions of high metabolic rate are electropositive, internally, to regions of lower metabolic rate. Tashiro<sup>21</sup> demonstrated a metabolic gradient as measured by CO<sub>2</sub> production in nerves. This gradient he found to be in the direction followed by nervous impulses within the cells and their processes. Alvarez<sup>22</sup> found that the spontaneous contraction rate of excised segments of intestine beating in Locke's solution falls progressively in passing from duodenum to terminal ileum. He later observed that this gradation of rhythm corresponds to a like gradation in CO<sub>2</sub> production of segments at rest and contracting,<sup>23</sup> and with the production of catalase<sup>24</sup> in the whole gastro-intestinal canal. He concludes that the direction of peristaltic waves in the gastro-intestinal tract follows underlying gradients of metabolism and that disturbances in peristalsis are related to alterations of local metabolic rate induced by trauma, poisons, inflammation, etc.



If the generalizations of Child be taken as a working hypothesis it must be assumed that there is normally an area in the renal pelvis whose metabolic rate is higher than that in any part of the ureter and that also there is usually a downward metabolic gradient from the pelvic to the bladder end of the ureter. But the difference between the metabolic rates at the two ends of the ureter must be so small as to be easily upset by abnormal conditions. It is not necessary to infer that, after its inauguration, the path of the peristaltic wave is constantly along a downward metabolic gradient. For example, in experiment 10, as noted above, the pacemaker for the whole ureter was in the renal pelvis; but after injury to the ureter at its middle, sufficient temporarily to cut off the lower half from stimulation from above, it became apparent that in this isolated segment the rate of metabolism was greatest at the distal end, thus causing retroperistalsis.

At the time of the first operation the accompanying vessels were carefully reflected before ligation of the ureter, so that the extrinsic blood and nerve supply should not be disturbed. Intrinsic blood supply and intrinsic nerves were doubtless functionally severed. Aside from this the dilated ureter differed from the normal ureter only in its reaction to distention, *i. e.*, (a) muscular hypertrophy, in most cases, (b) increased rate of peristalsis. (These peristaltic waves were sometimes incomplete.)

The conditions in the colon described by Cannon<sup>15</sup> in 1911 are reproduced in the hydro-ureter. His explanation of the rhythmical contraction inaugurated by the constriction ring in the gut was briefly as follows: There are three principal underlying factors: (a) A ring where the smooth muscle fibers were shortened and tonus increased, (b) distention, (c) refractoriness. Smooth muscle when in a short state is extended more readily by a moderate load than by the same load when it is in a long state.<sup>25</sup> The ring is stimulated to contract by distention, for withdrawal of the colonic contents stopped the pulsations while return of the contents restored them. Refractoriness to stimulation during contraction and the early part of relaxation was held to explain the rhythmicity.

The hydro-ureter is likewise a distended tube of smooth muscle which, like the colon, has an intrinsic innervation. This innervation of the ureter, however, is derived from the sympathetic system while that of the colon comes from the bulbosacral outflow.<sup>26</sup> Increased tonus and more rapid rhythmicity followed the local application of barium chloride to the ureter. What was the process?

Tashiro<sup>21</sup> found that stimulation of plant or animal tissue always caused increased CO<sub>2</sub> production. Barium chloride is a stimulant of smooth muscle. The process of oxidation is therefore made more rapid in the area of application. In other words, in the constriction ring, metabolic activity is increased and there must be a downward gradient of metabolism from the ring to all other parts of the ureter.

It may be urged that increased  $\text{CO}_2$  production and other evidences of cell activity are due only to a greater amount of work done in areas inaugurating peristaltic waves. But the cardia of the stomach does less work than the pyloric end, and yet Alvarez<sup>23</sup> found that, associated with its function of pacemaker and more rapid spontaneous contraction when excised, there was greater production of  $\text{CO}_2$  and of catalase in the cardia.

Increased tonus exists at the constriction ring in the ureter as in the colon, but more fundamental than this is an increase in the rate of tissue metabolism. Therefore the rhythm of the constriction ring may be attributed to (a) a higher rate of metabolism, (b) distention, (c) refractoriness.

The ureter deserves more careful investigation along these lines and a better understanding of the physiology of the normal and dilated ureter is of the utmost importance in clinical urology. It has been noted above that slight local trauma to the ureter causes a wave of contraction to be sent out in each direction from the injured area. Hyman<sup>20</sup> showed that *injured areas* have an increased metabolic rate and Segale<sup>27</sup> that *inflammation* is associated with increased biochemical cellular activity. It may be suggested that in the passage of a renal calculus it is quite possible that the injury inflicted by a sharp stone upon the ureteral walls may cause the inauguration, at this point, of waves of peristalsis and retroperistalsis. In addition to these isolated contraction waves, which are undoubtedly sent out thus from time to time, conditions are evidently reproduced clinically which in the above experiments caused the formation of a constriction ring. For in addition to increased local metabolism there must be a certain amount of distention following the action of the stone as a partial plug, especially after local contraction of the ureter about it. The kidney would continue to secrete urine until the intrapelvic pressure reached a point 40 to 50 mm. Hg below the blood-pressure.<sup>28</sup>

Trauma and inflammation about the stone are sufficient to cause a local increase in metabolic rate. With the appearance of distention all the conditions necessary for the creation of a constriction ring would be fulfilled. Lucas<sup>5</sup> demonstrated that, normally, the action of the ureter will provide for a neutral or negative pressure of urine in the kidney pelvis even against a resistance of 15 cm. of water pressure. He reported that he had seen the middle portion of the excised ureter of a small dog raise a column of water 72 cm. If, then, retroperistalsis were produced by a constriction ring as suggested above a considerable degree of pressure could be induced in the pelvis.

This would seem a more plausible cause of renal colic than local irritation or supposed ureteral efforts to dislodge the stone or only the passive dilatation of the pelvis by the secretion of urine against

back pressure from a plugged ureter. Osler,<sup>29</sup> describing renal colic from personal experience, speaks of "flushes or rushes of hot pain at intervals, often momentary, usually passing to the back, less often toward the groin." Also during pyelography, when the radiographic fluid is introduced into the pelvis under pressure through a ureteral catheter, patients frequently complain that the pain induced is similar to renal colic.

The suggested sequence of factors causing renal colic is, then, (a) trauma and probable inflammation of the ureter wall about the calculus, (b) contraction down upon the calculus causing temporary occlusion of the ureteral lumen, (c) increased pressure in the pelvis and ureter followed by moderate distention, (d) rhythmical contraction waves passing out simultaneously in both directions from the stone.

Definite proof that retroperistalsis occurs in renal colic cannot be offered, but the experiments reported above and the demonstration of constriction rings in the ureter make such a hypothesis worthy of careful consideration.

SUMMARY. Unilateral, incomplete ligations of the ureter were performed in a series of thirty-two rabbits and dogs. At a subsequent operation the ureters of the rabbits were observed *in vivo*. In the case of the dogs, after observation *in vivo*, both ureters were removed and placed in Locke's solution, where a ring preparation was made at either end of the intact ureter and contraction curves graphically recorded.

Extreme dilatation, more marked proximally, and in most cases hypertrophy of the muscle walls, resulted. In two cases the rubber band ligature cut through and the lumen of the ureter was restored.

In oxygenated Locke's solution it was possible to record the beginning and end of peristaltic waves which passed throughout the length of the ureter. These complete spontaneous waves originated at either end with equal frequency. In cases in which the segments of the two ends contracted independently the rate of the pelvic ring was, on an average, a little more rapid than that of the bladder end. There was no consistent difference noted in the size and form of the contraction curves at the two ends in either the normal or hydronephrotic ureter. The effects of certain drugs were noted.

Peristalsis in the unmolested ureter always began in the pelvis even in cases of extreme dilatation, in which fresh secretion of urine into the pelvis could not be a factor in causing the inauguration of the waves at this point. Mechanical or electrical stimulation of the ureter at any point caused a wave of contraction to pass outward in each direction. In one experiment trauma to the midpoint of the ureter produced a refractory area here which blocked waves from above. There then appeared waves of antiperistalsis arising near the bladder and passing upward to this block.

A crystal or drop of barium chloride applied to the hydronephrotic ureter *in vivo* caused a narrow ring of tonic constriction. From this, at a rapid rate, simultaneous waves of peristalsis and antiperistalsis passed out in both directions to the extremities of the ureter. This constriction ring is analogous to that described in the colon by Cannon.

**CONCLUSIONS.** The ureter is a muscular tube which, when subjected to partial obstruction, always dilates, usually hypertrophies, and whose peristaltic rate is increased.

Contraction waves pass in either direction with equal facility, depending on the location of the area whose rate of spontaneous contraction is most rapid. This area is normally in the renal pelvis, but under abnormal conditions a more rapid pacemaker may be established elsewhere. From the analogy to other axiate organs, it is suggested that underlying the more rapid rhythm of the pace-making area is the fact that its metabolic rate is more rapid than that in any other level of the ureter.

Production of a constriction ring which becomes pacemaker for the ureter above and below it depends on three things: the metabolic gradient, ureteral distention and refractoriness during contraction and the first part of relaxation.

It is suggested that in the passage of a ureteral stone, trauma and inflammation increase the rate of metabolism in the ureter wall about the stone, a constriction ring results, followed by distention of the ureter and retroperistalsis. This would cause great distention of the renal pelvis and give to renal colic its peculiar rhythmical character.

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## DIETS FOR THE AMBULANT TREATMENT OF DIABETES MELLITUS.

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THE modern treatment of diabetes mellitus in hospitals and sanatoria is a highly organized procedure. It demands the expert work of dietitians, laboratory technicians and especially trained nurses, in addition to medical supervision, and it requires the aid of a properly equipped laboratory and diet kitchen. By these means the diabetic, on leaving the hospital, has been taught, as a rule, how to examine his urine for sugar and diacetic acid, and has had some instruction in the principles underlying his diet. But for the uneducated patient, even after such a training, it is exceedingly difficult to devise menus with specified amounts of protein, fat and carbohydrate according to his needs, nor can the workingman or woman easily spare the time required for this important task. The rich, as a rule, solve the problem by putting a specially trained nurse in charge, but for the poor it is often impossible to meet the requirements of the situation.

The following lists have been prepared in order to bring weighed



TABLE II.—MEAT AND FISH PORTIONS FOR USE WITH THE MINIMAL FAT, STARCH-FREE DIET.

		Ounces of food weighed raw.					
MEATS:	Portion.	A	B	C	D	E	F
Beef—Soup meat, fore-shank, lean		3	4½	7½	9	11½	14½
Dried beef . . . . .		1½	2½	4½	5	6½	8½
Lean round steak . . . . .		2½	3½	5½	7	9½	11½
Lean roast beef (no visible fat)		2½	3½	6	7	9½	11½
Kidney . . . . .		3	4½	7½	9	12	15
Chicken . . . . .		3	4½	7½	9	12	15
Lean leg of lamb (no visible fat)		1½	2½	4	5	6½	8½
Tripe . . . . .		5½	8½	14	16½	22	27½
Lean veal (no visible fat)		2½	4	7	8	11	13½
FISH (Fresh only):							
Bluefish . . . . .		4	6	10	11½	15½	19½
Codfish . . . . .		4½	6½	11	13	17½	22
Flounder . . . . .		5½	8½	14	16½	22	27½
Haddock . . . . .		4½	7	11½	14½	19	23½
Sea bass . . . . .		4½	6½	10½	12½	16½	21
Sheepshead . . . . .		3	4½	7½	9	12	15
Smelts . . . . .		4	6	10	11½	15½	19½
Weakfish . . . . .		3½	5½	9½	11	14½	18½

TABLE III.—LIST OF VEGETABLES TO BE USED IN BOTH THE MINIMAL FAT AND LOW FAT DIETS.

Asparagus	Onions, cooked
Asparagus tips	Pickles, sour or dill
Brussels sprouts	Pumpkin
Cabbage	Radishes
Cauliflower	Rhubarb
Celery	Sauerkraut
Cucumbers	Sorrel
Egg plant	Spinach
Endive	Stringbeans
Greens from beets	Swiss chard
Kohlrabi	Tomatoes
Leeks	Watercress
Lettuce	Wax beans

The minimal fat diet is graded by 250 calory steps from 500 to 1500 calories. It is not feasible to increase the diet beyond this point, because when proteins make up the greater part of the nourishment, as they necessarily do in the minimal fat diet, the bulk of food becomes too great. It is even problematical whether all patients can consume the amounts designated under the 1250 and 1500 calory diets. However, the safest way to curtail the food in diabetics suffering with severe acidosis or threatened coma is first to restrict the fats. By means of the present list (I, II and III), this can easily be done. Carbohydrates may be added if it is thought advisable.

TABLE IV.—LOW FAT, STARCH-FREE DIET.

BREAKFAST:	Calories.	500	750	1000	1250	1500	1750	2000
Black coffee or plain tea (no sugar) as desired . . . . .								
Eggs . . . . .		1	1	1	2	2	2	2
Meat or fish (see Table V for kind and amount) portion . .	A	B	B	C	D	E	F	
Butter, flat teaspoonful . . .	none	1	1	2	2	3	3	
DINNER:								
Clear meat broth, plain, as desired . . . . .								
Meat or fish, from list, portion	B	D	E	E	F	F	F	
Vegetables, from list, ready to serve, heaping tablespoonsful	4	4	5	6	6	6	6	
Pot cheese, heaping tablespoonsful . . . . .	none	none	none	none	none	1	1	
Olive oil, teaspoonsful . . . .	none	none	2	2	2	3	3	
Butter, flat teaspoonsful . . .	1	1	2	2	2	3	4	
Black coffee or plain tea (no sugar) as desired . . . . .								
SUPPER:								
Clear meat broth, plain, as desired . . . . .								
Eggs . . . . .	none	none	none	none	1	1	2	
Meat or fish, from list, portion	B	D	E	E	F	F	F	
Vegetables from list, ready to serve, heaping tablespoonsful	4	4	5	5	6	6	6	
Butter, flat teaspoonsful . . .	1	1	1	2	2	3	4	
Black coffee or plain tea (no sugar) as desired . . . . .								
SPECIAL ORDERS:								
Saccharin, if desired, five tablets or less in a day.								
No extra butter, oil or fat to be used in cooking.								

For practical purposes of rough measurement the table and teaspoonful portions are adequate and exact within a reasonable margin of error. The portions of meat and fish are calculated to within the nearest  $\frac{1}{4}$ -ounce value. One-quarter ounce is probably closer than the average scales of the butcher or home can weigh accurately, but in giving the amounts in these fractions an indication is furnished on what side allowances should be made. The actual use of these diet lists is self-explanatory.

A concrete idea of the proportion of proteins and fats in these diets may be gained from Tables VI and VII. In the minimal fat diet the ratio of protein to fat is found to be about 3 to 1 when round steak is eaten as the meat or fish, and 17 to 1 when blue fish is used (Table VI). This, in either case, furnishes a very low fat intake. When the lowest possible quantity of fat is required it is evident that fish is more desirable than meat.



TABLE V.—MEAT AND FISH PORTIONS FOR USE WITH THE LOW FAT, STARCH-FREE DIET.

		Ounces of food weighed raw.						
MEATS:	Portion.	A	B	C	D	E	F	
Bacon, fried, fat thrown away . . . . .	1½	1½	2½	3	3½	5		
Brain . . . . .	2½	3	3½	6	7½	9½		
Chicken (to be boiled or broiled) . . . . .	2½	3	5½	6	7½	10		
Chicken (to be roasted) . . . . .	1½	1½	2½	2½	3½	4½		
Corned beef . . . . .	1	1½	2½	2½	2½	3½		
Dried beef . . . . .	1½	1½	3	3½	4½	5½		
Duck . . . . .	1½	1½	2½	2½	3½	4½		
Ham, smoked (to be boiled or broiled) . . . . .	1	1½	2½	2½	3	4		
Guinea hen . . . . .	2	2½	4½	4½	5½	7½		
Kidney . . . . .	2½	3	5½	6	7½	10		
Lamb chops . . . . .	0	1	1½	2	2½	3½		
Lamb (to be roasted) . . . . .	1	1½	2½	2½	3	4		
Mutton (to be boiled) . . . . .	1½	2	4	4½	5½	7		
Mutton chops, lean . . . . .	2½	2½	4½	5½	6½	8½		
Mutton (to be roasted) . . . . .	1	1	2	2½	2½	3½		
Pork (to be roasted) . . . . .	1½	1½	3	3½	4½	5½		
Pork chop, lean (to be broiled) . . . . .	2	2½	4	4½	5½	7		
Roast beef . . . . .	0	1	1½	2	2½	3½		
Soup meat, fore-shank, lean (to be boiled) . . . . .	2½	3	3½	6	7½	9½		
Squab . . . . .	1½	1½	3	3½	4½	5½		
Steak, round, lean . . . . .	2	2½	4½	4½	5½	7½		
Steak, sirloin, lean . . . . .	1½	2	3½	4	5	6½		
Tongue, fresh (to be boiled) . . . . .	1½	2½	4	4½	5½	7		
Tongue, boiled, smoked, cold . . . . .	1	1	2	2½	2½	3½		
Veal, roast or chop, lean . . . . .	2½	2½	4½	5½	6½	8½		
		Portion.	A	B	C	D	E	F
FISH (Fresh, to be boiled or broiled):								
Bass, black . . . . .	3	3½	6½	7	9	11½		
Bass, sea . . . . .	3½	4½	7½	8½	10½	13½		
Bluefish . . . . .	3½	4	7½	7½	9½	12½		
Butterfish . . . . .	1½	2	3½	4	5	6½		
Codfish . . . . .	3½	4½	8	8½	11	14		
Flounder . . . . .	4½	5½	10½	11	14	18		
Haddock . . . . .	4	4½	8½	9½	12	15½		
Halibut . . . . .	2½	2½	5½	5½	7½	9½		
Kingfish . . . . .	3½	4	7½	8	10	13		
Mackerel . . . . .	2	2½	4½	5	6½	8		
Perch . . . . .	3½	4½	7½	8½	10½	13½		
Pike . . . . .	3½	4½	8	8½	11	14		
Porgy . . . . .	2½	2½	5½	5½	7½	9½		
Salmon . . . . .	1½	1½	3	3½	4½	5½		
Sheepshead . . . . .	2½	3	5½	6	7½	9½		
Smelts . . . . .	3½	4	7½	8	10	13		
Weakfish . . . . .	3	3½	6½	7½	9½	12		
Whitefish . . . . .	4	4½	8½	9½	12	15½		
CANNED OR SMOKED:								
Herring, smoked . . . . .	1	1½	2½	2½	3	3½		
Salmon, canned . . . . .	1½	1½	3½	3½	4½	5½		
Sardines in oil . . . . .	1	1½	2½	2½	3	4		
Sturgeon, smoked . . . . .	1½	1½	3	3½	4	5½		
Tunnyfish in oil, canned . . . . .	1	1½	2½	2½	3	4		

TABLE VI.—APPROXIMATE QUANTITIES OF PROTEIN, FAT AND CARBOHYDRATE IN THE MINIMAL FAT, STARCH-FREE DIET WHEN ROUND STEAK OR BLUEFISH ARE USED AS MEAT OR FISH.

Minimal fat diet when round steak is used as meat or fish.	Protein, gm.	Fat, gm.	Carbohydrate, gm.
500 calories . . . . .	60	20	18
750 " . . . . .	93	33	18
1000 " . . . . .	126	43	21
1250 " . . . . .	159	54	24
1500 " . . . . .	194	66	25
When blue fish is used as meat or fish.			
500 calories . . . . .	88	4	18
750 " . . . . .	148	8	18
1000 " . . . . .	193	12	21
1250 " . . . . .	244	14	24
1500 " . . . . .	298	18	25

Table VII gives the relative values of protein, fat and carbohydrate when roast beef, round steak or flounder are used as the meat or fish in the low fat diet. These particular foods were selected because they represent a high, average and low fat content for these diets. When roast beef is eaten the fat is higher than the protein; with the flounder the ratio is reversed. The low fat diet, when the patient chooses his own food, has been calculated and found to contain, as a rule, proteins and fats approximately equal gram for gram.

TABLE VII.—APPROXIMATE QUANTITIES OF PROTEIN, FAT AND CARBOHYDRATE IN THE LOW FAT, STARCH-FREE DIET WHEN ROAST BEEF, STEAK OR FLOUNDER ARE USED AS MEAT OR FISH.

Low fat diet when roast beef is used as meat or fish.	Protein, gm.	Fat, gm.	Carbohydrate, gm.
500 calories . . . . .	22	39	12
750 " . . . . .	33	71	12
1000 " . . . . .	39	83	15
1250 " . . . . .	50	106	17
1500 " . . . . .	66	126	18
1750 " . . . . .	75	149	19
2000 " . . . . .	85	169	19
When steak is used as meat or fish.			
500 calories . . . . .	44	29	12
750 " . . . . .	72	44	12
1000 " . . . . .	87	64	15
1250 " . . . . .	105	83	17
1500 " . . . . .	134	97	18
1750 " . . . . .	147	118	19
2000 " . . . . .	164	136	19
When flounder is used as meat or fish.			
500 calories . . . . .	73	16	12
750 " . . . . .	122	22	12
1000 " . . . . .	149	37	15
1250 " . . . . .	172	52	17
1500 " . . . . .	217	59	18
1750 " . . . . .	235	77	19
2000 " . . . . .	259	92	19

In the low fat diets there is no difficulty, as far as bulk of food is concerned, in consuming as much as 2000 calories. As Mosenthal and Clausen<sup>1</sup> have shown a carbohydrate-free diet of 1500 to 2000 calories, containing approximately the same proportion of protein and fat as the present list, will maintain the nitrogen equilibrium of the diabetic and may be considered to furnish the patient with enough food to make him mentally and physically efficient. If the carbohydrate tolerance of the patient permits of a still further increase in the food it is best to add starch-containing foods and not proteins or fats.

The above food lists are presented in the belief that they will furnish a practical means of regulating the diet of sufferers from diabetes mellitus who are not receiving hospital treatment, and who, while under medical supervision, are dependent upon their own resources for the details of dietetic control. These diets are not intended in any way to supplant the more accurate and ideal means of weighing and measuring food if these are available.

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## ACUTE INFECTIOUS ENTERITIS WITH A POLYNEURITIC SYNDROME.

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THE action of bacterial poisons upon the peripheral and central nervous system is a source of great interest to the neuropathologist whether he be applying principles or producing lesions experimentally. One has only to recall that most serious epidemic of poliomyelitis in New York in the year 1916 to recognize the vast importance of how rapidly an infection may attack the central nervous system, and yet sufficient data is lacking in regard to the exact etiology and the mechanism of the action of the virus still remains unexplained.

The obscurity which surrounds the cause of many of the inflammatory processes which attack the various systems, gastro-intestinal, nervous, etc., as is seen in practice in institutions, is a fact which one must admit. There is hardly an institution throughout the

<sup>1</sup> Arch. Int. Méd., 1918, xxi, 269.

country which, at some time or other, does not have an epidemic of "asylum dysentery," "amebic dysentery," "pellagra" or what not. But the epidemic here under discussion, as observed by Dr. Harrington and myself in the summer of 1917, at the State Hospital for Mental Diseases, at Howard, Rhode Island, warrants comment, not only from the standpoint of the clinical picture, as one of an infectious enteritis with a polyneuritic syndrome, but also from the standpoint of its mechanism, as pointed out by its pathology, both clinical and tissue. A statement will also be made as to the possible selective action of certain bacteria, especially so in variable phases of their evolution.

Orr and Rows have offered much valuable data as to the lymphogenous infection of the central nervous system, and Rosenau has emphasized the possibility of the selective action of bacteria which bears, probably, a close relation to the various stages in its evolution. Much experimental work has been performed in an attempt to demonstrate the relation of the lymph stream to the peripheral nerves and to the spinal cord itself. In 1902 Homan and Laitnen injected streptococci into the sciatic nerves of animals, and was able to trace the bacteria into the meninges of the cord. Pirrone, in 1905, used as his infective agent the pneumococci and found changes in the cord limited to the side corresponding to the infected nerve. These investigators, therefore, concluded there must be a common lymph system for the posterior roots, the posterior columns and pia covering them, and that the lymph flows freely in the various channels between the fibers and other structures. It is upon this basis that syphilographers have based their conclusions in relation to the origin of tabes: that is, the syphilitic infection or toxin makes its entrance into the lymph stream and passes along the nerve trunks to the posterior roots and thence to the posterior columns. However, actual data as to this mechanism has not been thus far demonstrated, and is held only on theoretical grounds.

Homan's investigations, however, are still convincing in this point. Twenty-four hours after the injection of the bacteria into the sciatic nerve (streptococci) it is found that they accumulate in the lymphatic space situated on the internal surface of the perineurium, and that this can be traced along to the internal surface of the capsule and the spinal ganglia, then along the inner surface to the spinal roots and into the meninges, from which they spread into the peripheral zone of the cord, and especially so along the posterior median septum. Throughout this entire invasion there is an accompanying inflammatory reaction which, pathologically, might be considered an ascending inflammatory perineuritis. These experiments and conclusions call into play many theories regarding such processes as herpes zoster, anterior poliomyelitis, which is an acute inflammation of the anterior horn cells, and beriberi, which is a polyneuro-myositis of the toxic type. Of course, it must be duly considered

that in experimental work, in order to bring about distinct changes in the tissues, there is undoubtedly a possibility of the diffusion of inflammatory processes along the nerves to the central nervous system; but even admitting such a condition as a diffusion, it is of rather minor importance as compared with the fact that these organisms and toxins do reach the central nervous system, and that they probably make their way there through the lymph channels.

It is a rather interesting coincidence, in reviewing the literature, to find that Orr and Ross, in performing their experiments, used as their bacterium the staphylococcus. The series of cases that followed at the State Hospital, in the recent epidemic, also in a large percentage of cases examined, showed the presence of staphylococcus. Orr was able to cultivate, after repeated injections, a strain of staphylococcus whose virulence was very marked and whose activity upon the tissues was extreme. It is a well-recognized fact that the *Staphylococcus aureus* varies greatly in its virulence and that the virulence of even one strain may be enhanced or decreased in its passage through the individual's body. A prolonged cultivation will decrease its virulence. Here, again, experimentally, various forms of visceral lesions have been produced by inoculation. Rosenau has produced endocarditis, myositis, neuritis and other acute inflammatory processes in various parts of the human body by the inoculation with strains of streptococcus as well as staphylococcus of a prolonged cultivation, and he is of the opinion there are stages in the evolution of all bacteria which will produce a body reaction for that particular stage in which it happens to enter the body.

In experimentation, either by the lymphogenous or the hematogenous paths, one of two types of inflammatory processes may occur: one an acute inflammatory reaction with secondary degeneration, probably due to the extreme diffusion of the lesion, and the other an acute degenerative process, primary type.

The writers present this paper as the clinical and pathological report of a series of cases of infectious origin which occurred during the interval from July 15 to August 6, 1917. The highly infectious or communicable nature of the disease process was not apparent at its start, because the clinical symptoms lacked uniformity. The daily increasing number of cases, however, with the acute gastrointestinal symptoms and the accompanying involvement of the nervous system in a number of instances, made it obvious that one was dealing with a serious condition, and one, probably of an infectious type. As soon as this became apparent, arrangements were made to isolate and quarantine in two wards, which were prepared for this purpose, all cases believed to be suffering from this disease.

A systematic investigation was begun immediately in an endeavor to discover any cases which might exist throughout the wards of the hospital. This may account in some degree for the recognition

of additional cases during the last week of July and the first week of August, but the acuteness of the symptoms and the complaints of more receptive patients, who became affected, aided us materially in discovering instances of the trouble.

Forty-seven patients and four employees were quarantined. There were twenty other individuals whose symptoms were so mild that they were regarded only as suspicious cases; it is possible that they may have been mild or abortive instances of the disease. These later cases made a prompt recovery.

A watch was kept for the outcropping of cases on the male side of the hospital, but none came to light. Therefore, all the cases of the disease herewith described were in women patients.

The general onset of the clinical symptoms were acute gastro-intestinal disturbances, characterized by nausea and vomiting, frequent discharges from the bowels, containing mucus, or in some both mucus and blood; there was a rise in temperature to  $100^{\circ}$  and as high as  $104^{\circ}$ . In a large number of the cases there was great prostration, with headache and backache. The neuritic symptoms presented what appeared to be a peripheral neuritis, involving either the lower extremities or merely the upper extremities, and yet in a number of cases both the upper and lower extremities seemed to be involved. In these regions there was excessive pain on slight pressure in some of the cases, while in others there was pain over the muscles and nerve trunk only on deep pressure. In several cases the fear of being touched would cause the patient to cry out and the slightest brushing of the bed-clothes or touch of a camel's-hair brush caused excessive pain. The reflexes, especially the patella, were absent on both sides as a general rule, but in a few cases only on one side. The Achilles reflex was absent on one or both sides. With regard to walking and the coördinative mechanism there was great weakness. Some could stand only with help, but could not walk. In those whose upper extremities were affected there was a clumsiness in the use of the arms and hands. In a few cases there was a complete paralysis of the lower motor neuron of both the upper and lower extremities.

The early cases were the most severe and showed the slowest improvement. They were more uniform in their clinical manifestations after the disease process was once recognized than the later ones were. The early cases showed, to a marked degree, the neuritic symptoms as well as the gastro-intestinal. In the later cases the main force of the disease seemed to be exerted either on the gastro-intestinal tract or on the nervous system.

It seemed feasible to divide the cases which were isolated and quarantined into three groups, clinically considered. In the first group would fall 19 cases in which the gastro-intestinal symptoms were well marked, even severe in some instances, and in which the neuritic syndrome was also especially prominent. In the second

group were 7 cases in which the gastro-intestinal symptoms were serious and in 1 fatal, but in which the neuritic symptoms, while unmistakably present, were less so in degree than in the first group. In the third group were 21 cases in which the gastro-intestinal disturbance was the feature of the disease and only a few disclosing little or no evidence of a peripheral neuritis. Brief comment will be made on a number of these cases.

CASE I.—A. M., aged forty-five years; cook in the staff kitchen.

Patient had been complaining for two days before she made her illness known to a physician. Symptoms were vomiting, profuse bloody diarrhea; could retain no food in her stomach. All superficial reflexes were absent; there was pain along the course of the peripheral nerves. She entered into a state of coma on the sixth day of her disease, which was followed, in a few hours, by death.

Autopsy showed a marked congestion of the superficial veins along the greater curvature of the stomach, with areas of hemorrhage throughout the course of these veins. At the cardiac end of the stomach there was an area encircling the stomach, 2 cm. in width, presenting marked congestion and many small hemorrhages into the stomach. The intestines also showed an acute congestion throughout. The lower bowel, however, showed less evidence of congestion, but was spotted throughout its entire length by many petechial hemorrhages. The liver showed many areas of focal necrosis. The remaining viscera evinced nothing pathological.

CASE II.—R. K., aged fifty-two years; a patient helper in the staff kitchen; working with the above-described case in the morning. She was taken ill at about the same time with nausea; frequent evacuations of her bowels contained only mucus, with great prostration. There was marked tenderness over the superficial nerves of both upper and lower extremities. The patella and Achilles reflex, however, were present; abdominal and epigastric reflexes were absent. The temperature never went above 100°. The patient was unable to walk or use her arms. She continued in this condition for a month, when the clinical symptoms gradually disappeared, leaving her with a residual of an upper and lower peripheral palsy.

CASE III.—C. C., aged sixty-five years; the patient was taken sick suddenly with a temperature of 103.8°; vomiting; bloody mucous bowel movements. Her superficial reflexes of the lower extremity were absent. She could bear no weight on her feet nor allow the bed-clothes to touch her lower limbs. She became more and more prostrated and exhausted, and died on the twelfth day of her disease. The autopsy findings were the same as those described in Case I, with the lesions confined to the intestinal tract and liver.

CASE IV.—M. C., aged twenty-seven years. The patient became ill, with a temperature of 100°, associated with vomiting and profuse diarrhea of a blood-stained type. She was in the state of

collapse within a few hours after recognition of her disease. She then manifested a flaccid paralysis of the lower extremity, with a double foot-drop. All superficial reflexes were absent. There was marked tenderness over the peripheral nerve trunks and muscles of the lower extremity. During the first six days she showed rapid emaciation. On the eighth day of her disease her temperature dropped to 98°. On the ninth day her temperature rose to 101° and gradually increased, so that on the fifteenth day of the disease it was 105°, and was followed by death. The autopsy in this case showed marked injection of the vessels of the upper part of the small intestine.

CASE V.—M. McC., aged fifty-six years; patient was taken sick with a temperature of 101.5°; the bowels were loose, containing shreds of mucus and traces of blood, which increased during the second and third day. Aside from absent patella and Achilles reflexes there was no evidence of a peripheral neuritis. Patient died on the eighth day of the disease. No autopsy.

CASE VI.—M. C., aged sixty years; onset of the disease recognized by a temperature of 103.2°; vomiting; stools diarrheal, containing mucus and blood. Patella and Achilles reflexes absent, but no objective evidence of acute inflammatory peripheral neuritis. Death occurred on the fourteenth day. No autopsy.

CASE VII.—K. H., aged fifty-seven years. Onset of the disease recognized by temperature of 102°; diarrheal bowel movements contained a large quantity of mucus. Patella and Achilles reflexes absent, but no other evidence of peripheral neuritis. She died on the ninth day. No autopsy.

CASE VIII.—I. D., aged fifty-six years. Disease initiated by rise of temperature to 102°, associated with vomiting and diarrhea. She complained of marked headache, backache and cried out with pain in her feet and legs and said she could not use her arms or legs. She could not stand or walk. All reflexes were absent (superficial), in both upper and lower extremities. At the end of the first month she manifested only the residuals of a multiple neuritis. Her hands were clumsy, showing an inability to coördinate, especially in eating. (At the present time the patient is helpless, cannot walk; shows a double foot- and wrist-drop and is only able to do a few small duties with her hands.)

CASE IX.—K. T., disease initiated with a rise of temperature to 100°, diarrhea and vomiting. She could not walk or stand; moved her limbs with great difficulty, as if they were stiff, and complained of nerve and muscle tenderness. The legs and feet were cold and markedly manifested venous congestion. The patella reflex and Achilles reflex were absent. Three weeks after the onset of the disease she showed a recovery, as far as its acute manifestations were concerned, but there was present marked incoördination in both upper and lower extremities. Two months after the onset of the



disease the patient showed complete recovery, with a disappearance of her double foot- and wrist-drop, but she maintained a loss of her superficial reflexes.

CASE X.—M. P., aged thirty-seven years. The disease began with vomiting; bloody diarrheal stools; marked prostration. She complained of severe headache and backache, with pains in her legs on pressure and marked tenderness along the peripheral nerves of both upper and lower extremities. All the superficial reflexes in both the upper and lower extremities were absent. The acute manifestations of the disease disappeared by the eighth day. The patient's convalescence was interrupted, with a complete recovery from her neurological symptoms.

CASE XI.—M. S., aged forty years. Patient's disease process was initiated by a temperature of  $103.6^{\circ}$ ; nausea and vomiting; bloody diarrheal stools. These gastro-intestinal symptoms lasted fifteen days. During this time tenderness along the nerves and muscles in the lower extremities was manifest. The superficial reflexes of the lower extremity were greatly diminished. At the end of the twenty-first day the patient began to improve and her convalescence ended in a recovery of both the gastro-enteric and neurological symptom-complex.

CASE XII.—A. McG., aged thirty-six years. The disease began with a temperature of  $103^{\circ}$  and marked vomiting. The bowel disturbance, however, was slight. There was marked tenderness over the peripheral nerves of the lower extremities, with a loss of both patella and Achilles reflexes. The duration of the disease was eleven days, followed by a complete recovery.

CASE XIII.—C. H., aged sixty years. Initial temperature rise  $104^{\circ}$ , associated with a diarrhea that continued for seven weeks. There was marked tenderness over the peripheral nerves of the left lower extremity only. The patella reflexes were present on both sides, however. The Achilles also were present. The patient made a slow but gradual recovery.

CASE XIV.—M. G., aged thirty-eight years. No rise in temperature. Repeated attacks of vomiting. Bowels diarrheal in type, but no blood or mucus. He complained of great pain in the left leg. There was marked tenderness along the peripheral nerves of both extremities. The superficial reflexes of the lower extremities were absent and the left foot showed a distinct drop. This patient made a slow recovery.

CASE XV.—S. T., aged fifty-nine years. Onset of the disease manifested by a temperature of  $100^{\circ}$ . During the first three weeks of the patient's illness there was marked constipation. During the next few weeks there was an acute gastro-enteritis. During the entire disease process, however, the patient was very sick, complaining of a great deal of pain in the upper and lower extremities and the annoying symptom of frequent attacks of sneezing. During

the second week of the disease process the peripheral neuritis became complete, so that the patient had a well-marked double foot- and wrist-drop. The superficial reflexes in both the upper and lower extremities were absent. During the fifth week of the disease atrophy of the muscles of both the upper and lower extremities began to be manifest, which continued to a marked degree so that at the present time the patient is utterly helpless.

In the cases in question the sudden outbreak of an acute gastro-enteritis naturally leads one to the opinion that said infection must have been introduced *via* the gastro-intestinal tract. It therefore seemed plausible to obtain cultures from milk, which is one of the staple articles of diet in ward patients. Cultures from the milk as it came from the dairy were made and a rapidly growing staphylococci made its appearance in twelve hours. These cultures were grown on both plain and 3 per cent. glycerin media. Bacterial count was also made and found to contain several millions per cubic millimeter.

It therefore was assumed that a virulent, rapidly growing staphylococcus was introduced into the gastro-intestinal tract. Cultures were then made from the nose and throat and excreta. Here, again, rapidly growing colonies of staphylococci were obtained. It might be stated, however, that in several cases the pneumococci and streptococci were grown from the throat and nose cultures in the first twelve hours, but they were quickly overgrown by a staphylococci which finally outgrew the streptococci and pneumococci. Cultures obtained from the blood of several patients also showed a growth of staphylococcus at the end of eighteen hours. Here, again, in one case, at the end of twenty-four hours, the colony growth resembled, morphologically, the pneumococci. When regrown, however, upon transplantation, it assumed the characteristics of the staphylococci and grew out at the end of forty-eight hours as a pure culture of *Staphylococcus aureus*. Catheterized specimens of urine made with the same result in the majority of the cases examined, namely, a final growth of *Staphylococcus aureus*.

Up to this time one must conclude that the source of infection was milk; that the agent was the staphylococcus; that the mode of entrance was *via* the gastro-intestinal tract with an acute gastro-intestinal reaction, as manifested by the symptoms, vomiting, marked gastric pain and distress, with profuse bloody diarrhea. During this acute infective stage there was the concomitant rise in temperature and in some cases an acute delirium and excitement lasting over several hours. Thus far clinically and clinicopathologically the signs and symptoms are indicative of an acute infection of staphylococcus type.

The question was then raised: What relation did the neurological signs, which made themselves manifest within the first twenty-four hours, bear to this acute infection? Blood analyses as above noted

yielded the staphylococcus; therefore there must have been a staphylococcus bacteremia—a hematogenous infection.

Absorption from the intestinal tract as proved by experiments shows conclusively that derivatives of food products are transmitted directly to the blood-capillaries, and that any interference with the lacteal circulation does not interfere with the absorption, especially of proteid products. Biologically, bacteria are of a protein make-up. Their absorption or transmission from the intestinal system to the vascular system would therefore undoubtedly occur through the capillaries and thus make an entrance into the general circulation. After entering the circulation the selective action of the bacteria, according to Rosenau, would take place and in the series of cases above reported it is evident that their activity was directed toward the peripheral nervous system, for somewhat coincident with the acute infection there developed symptoms and signs suggestive of a peripheral polyneuritis. Out of this series of cases there were four which came to autopsy, and where it would require prolonged discussion to review each case by itself the examiner will summarize his findings. The changes in the viscera and peripheral nervous system were much the same in all cases and they will therefore be described as a group.

Macroscopically the intestinal tract showed an acute hemorrhagic gastritis and enteritis, the mucous membranes being deeply injected and showing small hemorrhages throughout its mucous coat.

The liver in all 4 cases showed indications of retrogressive metamorphosis; 1 case showed an advanced fatty degeneration with focal necroses and the remaining 3 cases showed distinct focal necrotic areas. The fact that in all 4 cases coming to autopsy there were observed focal necroses of the liver would distinctly point toward the fact that there must have been an acute systemic infection, for it is hardly possible to believe that these retrogressive changes noted were merely coincident to the general disease processes.

Sections of the peripheral nerves and of the mid-dorsal cord showed small hemorrhages between the nerve bundles both in the nerve itself and in the nerve roots as attached to the cord. There were also noted extravasations of cells between the individual fibers. Examination of the anterior horns for a disturbance in the motor cells, keeping in mind anterior poliomyelitis, gave negative results, and there were no indications of a hemorrhagic process in the horn itself.

To recapitulate: It would appear in summing up the entire situation that (1) there was introduced into the body an exogenous toxin (staphylococcus infection); (2) that it was introduced into the gastro-intestinal system and there produced an acute infective gastro-intestinal; (3) that there was a transmission of the infective agent from the intestinal tract to the general circulation, producing a septicemia (staphylococcus in type); (4) that for reasons still to

be explained, but to be constantly kept before one's attention, this particular infection had a selective action upon the peripheral nervous system and caused the symptom-complex known as peripheral polyneuritis; (5) clinicopathologically the milk, throat cultures, blood, fecal examinations and urinary tests for bacteria showed in general the staphylococcus; (6) pathologically there was observed an acute hemorrhagic gastro-enteritis, multiple focal necroses of infectious origin in the liver and acute hemorrhagic neuritis (hemorrhages between the nerve bundles).

Therefore, clinically and pathologically, the diagnostic grouping of these cases has been placed in the acute infective enteritis group with a polyneuritic syndrome.

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## FUNCTIONAL BLOOD-PRESSURE.

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IN contradistinction to those permanent or organic changes in the circulatory apparatus which signify their presence by a constant or stationary sphygmomanometric reading, hypertensive in character, and about which medical opinion accepts the rising valuations as of supreme clinical importance, there must also be recognized, and properly evaluated, a larger group of variations, primarily functional in nature, and which, while at times hypertensive in reading, are due to disturbances of a functional or physiological character.

This first type is understood as being organic or permanent and the latter as functional or transient.

The first is pathological and therefore a factor for serious concern; the latter is still considered as within the elastic bounds of the physiological and must be so interpreted, and therefore kept from passing over into the domain of the pathological.

The vital and essential principle always to be recognized when considering the importance of blood tension lies in this fact—this great truth—that the etiological factors causing this rise in the blood tension within the bloodvessels, numerous and diverse though they be, act by causing an elevation of the blood tension or pressure primarily, and only secondarily do the more permanent or organized changes follow as a result of the irritation or disturbances being long continued.

In the understanding of functional blood-pressure disturbances, as well as the arteriosclerotic changes in the bloodvessels, the structural elements or anatomy of the bloodvessel wall must be kept in mind.

The walls of the arteries consists of three coats, which, named from their relative position, are the inner, the middle and the outer. The structure and relative thickness of these coats or tunics vary in vessels of large, medium and small caliber.

The media or muscular coat is the thickest coat of the artery and the one upon which attention is focussed. It consists of many circular lamellæ of involuntary muscle fibers, intermingled with connective tissue, in which elastic fibers are conspicuous. This muscle tissue gradually attenuates as the capillaries are approached, until finally, in the capillaries themselves, no muscular fibers appear, only nucleated endothelial cells. Finally, the capillaries, by their union, constitute the capillary plexus, *i. e.*, the retia capillaria.

As regards the innervation, it is well to recall that the sympathetic, through its vasoconstrictor and its vasodilator fibers, maintain vessel tonicity.

Luciani<sup>1</sup> states: "There are, accordingly, constrictor and dilator nerves to the bloodvessels, the former corresponding to the systolic and the latter to the diastolic nerves of the heart. Vascular rhythm and tonicity are analogous to cardiac rhythm and tonicity."

Foster<sup>2</sup> says: "We have repeatedly insisted that the relaxation of a muscular fiber is as much a complex vital process, and as truly the result of the muscular substance, as the contraction itself, and there is *a priori*, no reason why a nervous impulse should not govern the former as it does the latter."

From the vasomotor center, then, is the tonicity of the vessel controlled. Thus, any influence, metabolic, endocrinologic, toxic or psychic, may affect the musculature of the vessels with the production of constriction, and this constriction, through the development of the muscular overaction, may result in the condition of hypertonus.

Through the action of localized contractions in the great splanchnic areas there may be a pressure rise (functional hyperpressure) or a fall through splanchnic relaxation.

Our reasoning thus leads us to the belief that a prolonged influence of the vasomotor controlling mechanism, through the agencies of faulty metabolism, etc., or by the production of overdevelopment of the muscular tissue in the walls of the arteries, with the resultant hypertonus, may also be at the foundation of the functional hypertensive blood-pressure.

Degeneration in the walls of the bloodvessels may develop without the production of a raised blood-pressure, but where it becomes a factor of danger, and of serious concern to the circulatory balance, it always follows this period of functional or physiological rise instead of preceding the same. Therefore, the fundamental feature for correction, and the great clinical value of this question

<sup>1</sup> Human Physiology, vol. i, p. 343.

<sup>2</sup> Text-book of Physiology, Part I, p. 313, 5th ed., 1888.

of blood-pressure, are to be found in this early knowledge of the disturbing elements in the blood stream, acting in the twofold relation of causing a primary elevation of pressure and associatedly a structural though an insidious change in the vessels themselves. As mentioned, these arterial changes and sclerotic lesions may develop in the peripheral vessels in the aging and aged even to the formation of calcareous plaques, as noted in the senile or decrescent type of arteriosclerosis described by Clifford Allbutt, without causing a manifest elevation in the arterial pressure. In contradistinction to this fact it may also be noted that a permanent hypertensive reading is frequently observed in persons about the fourth or fifth decade, in whom no outward evidence of arterial sclerosis can be discovered, though positive changes have taken place in the cerebral or splanchnic vessels. This condition has likewise been fully described by Allbutt and called hyperpiesis. Reference will be made to this condition later.

Between the great group of diffuse arteriosclerosis, chronic Bright's and hyperpiesis, with permanent organic and fixed hypertension and the great group of normal cases, so called because it is necessary to have an approximate standard even though the normal limit of flexibility may be greater than at present accepted, there lie two groups of functional blood-pressure conditions which may be termed:

1. Functional hypertensive blood-pressure cases.
2. Functional hypotensive blood-pressure cases.

A consideration of these two groups may be of value.

1. FUNCTIONAL HYPERTENSIVE BLOOD-PRESSURE. Our increasing knowledge of the dynamics of the circulation discloses the fact that pressure or tension, high or low, in the vessels are registered by the mercury manometer, and as recognized clinically, is a condition of functional variation which may affect the individual at all ages and under various circumstances of life. For instance, changes or variations may be brought about at different hours of the day; it may be influenced by the mental attitude or the type of diet and by emotion, especially anger, particularly when suppressed through ideas of dignity. This may so elevate the tension as to cause bronchial wheezing, and an asthmatic cough, especially where the tonicity of the cardiac musculature is subnormal. Strenuous exercise will raise while rest will lower the arterial tension.

Normal blood-pressure, it may be mentioned, is dependent upon a properly functioning vasomotor system; upon the integrity, strength and energy of the cardiac musculature; upon the normal elasticity of the arterial walls; upon the volume of the circulatory blood—its viscosity—and upon the peripheral resistance. Thus, anything that disturbs the physiological harmony of this mechanism will naturally influence or alter the mechanical agencies of its flow and so register a change in the blood-pressure or tension. Attention

has rightfully been called to the fact, by many authors, that this recorded pressure or tension is classed as a symptom and not as a disease. As a symptom it proves of inestimable value in the study of disease. It thus aids in the differential between the organic and the functional lesions.

Realizing, then, these functional variations in the manometric reading it is advisable to repeat the observations a number of times, and on different occasions, when making a study of hypertension. Take the pressure after eating, after exercise, and after a prolonged rest. It may be advisable for the observed patient to remain recumbent for a period of twenty-four hours, with strict attention to the diet, and with full intestinal elimination, before the final judgment is rendered.

If the case is functional, a marked reduction in hypertension is witnessed; if organic, no marked change results.

*Etiology.* It may well be asked and answered: What are the usual causes for heightened pressure? Usually due to errors of diet, eating and, previous to the advent of prohibition, drinking, long continued; combined with a life of worry, mental depression and emotion. In the largest number of cases, disturbances in metabolism, by which is inferred those forms of destructive metabolism whereby faulty end-products of digestion, toxic to the living somatic cells and vasomotor center, maintain a constant pressor effect, through irritation, with the eventual development of the productive changes in the cells themselves. Many persons observe little judgment in their gastronomic seances, with the resultant overwhelming of the system by the toxic products developed. Intestinal stasis, from whatever cause, with biliary deficiency, hasten the production and the absorption of these putrefactive toxic products.

*Auto-intoxication.* This resultant of the abnormal or destructive metabolism undoubtedly lies at the foundation of the hypertensive and arteriosclerotic alterations. Intense is the discussion surrounding this subject, and intensive are the efforts of the chemicophysical laboratories to fathom it.

Dr. Louis Faugeres Bishop,<sup>3</sup> in seeking to solve the "riddle of arteriosclerosis," develops a convincing case against auto-intoxication. To quote: "I believe (the key) is to be found in the still obscure field of biochemistry, and I believe in the end it will be discovered that the reason for the perfectly apparent increase of arteriosclerosis of modern time is to be found in the well-known changes with regard to the habit of people in connection with protein food and the different manner in which they are handled commercially, together with some factor or factors, yet to be analyzed, that render food idiosyncrasies of a low grade producing unconscious poisoning."

<sup>3</sup> Arteriosclerosis, 1915, p. 15.

Professor Victor C. Vaughan<sup>4</sup> discusses this problem from the standpoint of individual protein sensitization and anaphylaxis. He states from laboratory experience, "The protein poison is a powerful agent," acting against the vital somatic cells.

Luciani<sup>5</sup> quotes, as the result of the action of intestinal bacteria in their transforming action on the carbohydrates, fats and proteins, the following:

"On carbohydrates: By fermentation, the production of alcohol, lactic, benzoic, succinic, butyric and valerianic acids; also carbonic acid gas, methane or marsh gas and hydrogen gas.

"On fats: The production of glycerol and fatty acids.

"On proteins: The toxic putrefactive elements: proteoses, peptones and amino-acids. These amino-acids are very complex and subtle agents for good or for evil."

According to Lusk:<sup>6</sup> "One must know the life of sixteen amino-acids in order to be familiar with the metabolism of protein." These nitrogenous bodies, indol, scatol, phenol, pancresol, phenyl-propionic acid, etc., are toxic agents of very great moment. In addition, a group of chemical compounds, the so-called ptomains, appear; these little-known alkaloids are powerful agents of destruction."

With such in mind it is evident that if these products of putrefactive activity and metabolic decomposition acted suddenly they would very quickly overwhelm the vital resisting forces of the human organism. Therefore, when acting, in cases of intestinal stasis, very gradually and over long periods—decades—they produce the changes in arterial compensation and degeneration, with the production of this primary functional, and eventually a permanent or organic blood-pressure variation.

This is what is intended by the term destructive metabolism.

Other Causes: Endocrine disturbances, especially of the thyroid, with the association of hyperthyroidism, when long active, gradually produces an overacting heart; with the development of hypertrophic changes in both the cardiac musculature and the musculature of the walls of the arteries.

Blood-pressure observations, by calling attention to this state, may spare the organism from the terminal apoplexy or cardiac exhaustion.

Infectious Agents: The ubiquitous microbe, the bacterial organism and their toxic products undoubtedly act to the detriment of the somatic cells. Undiscovered areas of focal infection must be credited as etiological agents.

Syphilis and the metallic poison, etc., add to the list.

The hypertension of nephritis is assumed to be organic. Little

<sup>4</sup> AM. JOUR. MED. SC., February, 1913.

<sup>5</sup> Human Physiology, vol. iii.

<sup>6</sup> The Science of Nutrition, 3d ed., p. 175.



attention, therefore, is given to it under the heading of functional hypertension; still:

The etiology of this large class is unsettled, for while there are many theories the only one thoroughly confirmed is that of Janeway, Carrel, Sampson and Pearce, who proved that the reduction of the amount of kidney substance alone may cause hypertension.

Attention is directed to the fact that the early changes may to a degree be assumed to be functional. Thus the early use of the manometer would prove a safeguard against neglect or oversight and the ultimate evils attendant upon a true nephritis.

**Hyperpiesis:** Vitally important is it, in cases showing signs of high pressure, to early assign the condition to its rightful category. A class of cases very frequently met with during these days of strenuousness is the one so fully described by Clifford Allbutt, regius professor of physic in the University of Cambridge, England, and called by him hyperpiesis. It seems to be little understood by the profession at large. Allbutt defined this condition as a state or disease whose essential feature and earliest manifestation is hyperpiesis or elevated blood-pressure. Its causes probably fall within the category of etiological factors given. At first the response to the irritations causing the heightened pressure is wholly functional, but in the course of time, the causative factors still acting, it is followed by the cardiac hypertrophy and by the arterial sclerosis. It then is classed in the list of the organic high-pressure cases. My reason for introducing it here is to call attention to the undoubted fact that *early in its history it comes under the functional high-pressure classification, and so merits attention.*

Houchard calls this early period "the presclerotic state."

Clifford Allbutt states emphatically:<sup>7</sup> "If we catch hyperpiesis early, and keep at work against it, it can be cured more often than not." Occurring in people of apparent robust health, it progresses insidiously months and years before it is suspected. Only by the regular use of the sphygmomanometer can it be detected early. When the first symptoms of dyspnea, from the breaking down of the heart's reserve force, appear, or the presence of precordial or substernal oppression or pain is experienced, or a sudden attack of pulmonary edema upon exertion or symptoms referable to the cerebral vessels, *i. e.*, slight shock or warnings from vasomotor spasms, result, the process is well advanced.

A period of increasing nervousness, irritability or consciousness of the burden entailed in holding one's position in life, and a similar consciousness of a lessened ability to meet the same with undue fatigue, these register clinically the earliest signs and bespeak for recognition and a successful therapy. Thus: suspect the tendency to, or the presence of, hyperpiesis in every full-blooded, stocky man

<sup>7</sup> Diseases of the Arteries, Including Angina Pectoris, vol. ii, p. 81.

or woman of plethoric habits, active temperament and with hearty appetites at the period of the late middle life, between the ages of forty-five and fifty-five years.

*Climacteric Hypertension.* So deeply impressed is the profession with the thought that hypertension is synonymous with nephritis, and that even hyperpiesis must always be, to a degree, allied to chronic Bright's, that there hardly seems room in their thoughts for this essential truth about pressure: that functional hypertension can occur in many and diverse conditions.

I wish also to suggest that there is a type of high pressure frequently found in women at the period of the menopause. These cases do not show any evidence of arteriosclerosis and no obtainable evidence of nephritis, either in the blood or in the urine. The retinal picture is likewise normal. To this class, then, the term hyperpiesis hardly seems correct, because they develop during or subsequent to and are apparently closely associated with that complex function of ovulation and ovarian glandular secretion, with their influence over all bodily functions.

During this period of ovarian dysfunction, and especially following its cessation, these patients develop a group of unassociated symptoms, nervous, gastric and cardiac in origin, which cause them to seek relief. As a rule, they are healthy in appearance, rather obese, though not necessarily so; are active, nervous and inclined to worry. They are met with between the years of forty and fifty years. They have headache, vertigo, paresthesias, epistaxis, numbness or sleeping of the extremities. On examination they show a high arterial blood-pressure, usually about systolic 200 and diastolic 120 mm. Hg.

Under rest, diet, bromide sedation and endocrine medication a very pronounced drop in the pressure is obtained; to their very great relief.

Arthur H. Hopkins<sup>8</sup> has described a group of these cases. The condition might be more fully elaborated. Attention is directed to it for the purpose of classifying it among the functional pressures and to suggest that a routine blood-pressure examination be made in all women at the menopause seeking relief from the obscure symptoms enumerated above.

Do not call these cases hyperpiesis, rather climacteric high-pressure cases.

*Functional High Pressure in Obstetrics.* To the obstetrician the knowledge of functional blood-pressure is of the highest importance. The response of the arterial controlling mechanism to the toxins developed during pregnancy causes a hypertonic rise, which at once suggests the advent of a toxemia and foreshadows the advent of the dreaded eclampsia.

<sup>8</sup> AM. JOUR. MED. SC., June, 1919, p. 826.

It is well to recall that the normal blood-pressure in a normal healthy pregnant woman will average close to 118 mm. Hg, with a gradual increase in the later months.

During the early months of the pregnancy, with nausea and vomiting, the toxemia or endocrine imbalance may cause the pressure to fall a few points, especially in severe cases. My experience seems to warrant the belief that feeding these patients with ovarian glandular substance restores this fall.

But, and here is the factor of real importance: To every physician who cares for maternity cases it should be known that a high 150 to 160 mm. Hg reading and a rising pressure in the latter half of pregnancy, and especially so when associated with albuminuria, constitute, very often, the earliest signs of a toxemia, which may suddenly terminate in eclampsia.

This hypertensive blood-pressure is purely functional, for following the birth of the child, in eclampsia, usually within forty-eight to seventy-six hours the pressure will fall to figures approximating normal. Therefore, as far as it is possible to outline suggestions in maternity cases, the following is suggested:

Invariably, upon the acceptance of a maternity case, obtain the blood-pressure data and record the same. Throughout the early periods verify the findings monthly. In the latter half of the pregnancy a blood-pressure below 124 mm. Hg may be disregarded. A pressure reading, however, from 125 mm. to 150 mm. Hg needs very careful watching. A pressure over 150 mm. Hg, when the original normal pressure was about 120, is considered fraught with danger and needs very careful eliminative measures; and should it show a tendency to rise higher the induction of premature labor should be considered.

The role, therefore, of the sphygmomanometer in pregnancy is a very important one. As a corollary to the above, after delivery, in involved cases, the persistence of the high pressure must always be considered of moment and the case watched and treated until it falls to normal.

The modern scientific care of maternity cases, therefore, includes the routine use of the manometer, with a view to the recognition of the functional elevations proved of such supreme importance.

*Hypertension in Cerebral Hemorrhage.* In apoplexy the cerebral hemorrhage always causes a marked functional use to heights greater than the previously registered heights maintained by the organic causative factor. A recent case with original systolic pressure of 225 mm. Hg, diastolic 115 mm. Hg, prior to the hemorrhage, rose within one-half hour to the high figure of 285 mm. Hg systolic and 150 mm. Hg diastolic. The resulting coma continued until the pressure gradually fell to 230 mm. Hg systolic and to 130 mm. Hg diastolic, when consciousness returned.

*Hypertension in Typhoid Fever.* In the course of typhoid fever the pressure is liable to decline below the normal readings for the patient in health. A sharp rise in the blood-pressure accompanied by abdominal pain suggests perforation of the intestinal wall.

*Hypertension in Cerebral Growth.* A rising pressure is usually associated functionally with the headache, vomiting and papilledema of cerebral growths. Removal of the growth lowers the pressure.

2. THE FUNCTIONAL HYPOTENSIVE BLOOD-PRESSURE CASES. A very important group of cases showing hypotensive or depressive readings are frequent claimants for medical consideration. This condition, while not as spectacular as the hypertensive group, is no less important, and merits intensive study for its proper differentiation and treatment.

The condition is often associated in the minds of the physicians, and even of the patients themselves, with the idea of cardiac exhaustion; but while the inherent cardiac musculature may not be fully normal and is usually subnormal, still the lowered tone so evident is more likely due to deficiency of the vasomotor function from whatever constitutional cause. Constitutionality, then, is very evident in these subjects.

It is essential to remember, however, that a low arterial pressure may be practically normal for a particular individual, and it by no means follows that the arterial pressure is abnormal, because it is below the average level of pressure generally present in a healthy subject of the same age.

Cases are seen in early and middle life enjoying health and doing their work, in whom the arterial pressure has not exceeded 90 mm. Hg systolic and 60 mm. Hg diastolic. A very recent pregnant woman of twenty-four years showed a systolic reading of 85 mm. Hg and a diastolic reading of 50 mm. Hg. No complaint except indisposition to exertion was made. While this latter borders on the abnormal and prompted measures for its improvement, it is cited as evidence of the elasticity of the normal limits of pressure.

A hypotensive pressure must be considered functionally pathological, however, when conjoined with signs and symptoms of impaired health and sense of well-being.

Hypotensive cases may be separated into several groups:

1. The Tuberculous Group. Constitutional deficiency, through direct tuberculous inheritance, is a profound factor in depressive conditions.

Tuberculosis affects the vitality of the whole organism, hence the low readings. It is well, therefore, to always suspect a tuberculosis, active or latent, in those cases of young men and young women between the ages of sixteen and twenty-six years who, while showing wasting and anemia, have an associated hypotension.

## 2. Endocrine Deficiency:

A. Toxemic group.

B. Pituitary group.

A. *The Toxemic Group.* Recent studies of the dominance of the endocrine glands over the physical functions and the vasomotor balance have awakened intense interest in this specific group. This class of patients show no evidence of tuberculosis, look normal to casual observation, but suffer with a depression of their vital functions termed asthenia. They lack "pep," are easily tired and have no reserve. By force of will they may rise to the occasion for the time, but readily revert to the expressed state of fatigue. They are especially met with among young women who are relegated to the class of neurasthenics for the want of a better comprehension of their ailment. At the present time it is realized that asthenia or neuromuscular depression, with its hypotension, is really a condition of cellular intoxication. According to Henry Harrower, "If the regulating mechanism that controls the circulation, cardiac efficiency and blood-pressure is insufficient, then asthenia must result from the accumulation of the ordinary amounts of cellular waste." The chief cause of this group, with its asthenia, appears to be due to a condition of chronic toxemia from faulty oxidation and deficient elimination.

By the use of the products of glandular substances from the adrenal body, with its synergist the thyroid, augmented by lecithin elements a marked restoration of the proper functioning of these bodily organs lessens the asthenia and raises the pressure by the activating effect upon the vital functions themselves.

So marked is the benefit derived by this class of hypotensive cases that efforts should be made to recognize this type among the depressive groups. Whether or not adrenalin acts, *per se*, to raise blood-pressure the present opinion seems opposed to the theory. Experience, however, does show that the use of the suprarenal glandular substance, aided by other therapeutic measures, does so act on the psychonervous functions as to sustain them and eventually cause a restoration to more normal conditions.

B. *The Pituitary Group.* Again: Must deficiency of the endocrine elements be recognized as a provocation of not only low blood-pressure but also of a low constitutional state itself?

Dr. Walter Timme<sup>9</sup> describes a series of cases observed at the Neurological Institute of New York City, undoubtedly due to pituitary deficiency. These cases are constantly seen in practice, are not recognized, and are wrongly diagnosed and wrongly treated. They all suffer from some psychosis associated with their bodily deficiency. Timme refers to the condition as "A new pleuri-glandular compensating syndrome."

<sup>9</sup> Medical Clinics of North America, January, 1919.

They show symptoms of intratemporal headache, great fatigability, low blood-pressure (hypotension), skeletal growth abnormalities and usually sex deficiencies.

They are seen in both early, middle and late stages, or from adolescence to middle life.

This syndrome seems to involve the thymus, adrenal, thyroid, gonads and pituitary bodies.

Beginning in early life through a failure of the thymus function a necessary compensatory development of the other glandular bodies is imperative for the continuance of the organism. Seen first in youth some years before or after puberty it continues actively for a period of about twenty years.

The first symptoms are those of the thymicolymphatic state observed between the years of ten and fifteen. The second or compensatory pituitary state of puberty between ten and twenty; the pituitary gigantism state between twenty and thirty; and finally the developed state of acromegaly.

Low pressure is incident to all stages.

The functional character of this complex condition is evidenced by the marked general improvement following the feeding of these patients with pituitary gland products, a corresponding rise in the blood-pressure indicating the functional hypotensive nature of the vasomotor condition.

3. *Infectious*. Bacterial invasion of the body functionally depresses the vital activities, both by their presence and by the developed toxins. Influenza, pneumonia, diphtheria, typhoid, etc., are all associated with depressive readings. So profound may be the depression as to quickly overwhelm the organism.

Convalescence should be guided by the manometer in order to direct the activities of the patient.

4. Shock, hemorrhage, vomiting and diarrhea account for many low readings, the correction of the cause restoring the pressure.

5. With a view to the above outlined conditions it is evident that the functional aspect of the question of blood-pressure is a very important one, to be given consideration in every case of hypertension and hypotension before assigning the causative condition to that of the organic or permanent type; and that it is during the period of this functional development that therapeutics and associated methods of treatment warrant the expectation of success. Efficient treatment is dependent upon accurate diagnosis: To differentiate therefore, between the functional and the organic disturbances is the *sine qua non* of success.

## A STUDY OF THE BLOOD AFTER SPLENECTOMY: WITH SPECIAL REFERENCE TO THE LEUKOCYTES.

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(From the Department Laboratory, Southern Department, U. S. Army.)

SHORTLY before noon, July 28, 1919, a cavalryman at Fort Sam Houston, Texas, while caring for his horse after the usual drill, was seized with faintness, nausea and sudden sharp pain in the left upper quadrant of the abdomen. He was brought to the Base Hospital in a condition of collapse. A definite diagnosis was impossible, but six hours after the onset of symptoms a laparotomy was done, with the tentative diagnosis of a ruptured viscus. Hemorrhage in the peritoneum was traced to a small tear in the spleen and the organ was removed. The temperature was subnormal on admission, and except for a short time on the following day was never above 100°. The wound healed promptly and without infection. After the first few weeks the patient appeared completely restored to health, though at times a moderate tachycardia was noted. He stated that he weighed more than ever before. The Wassermann reaction was negative, and before his discharge repeated examinations failed to reveal any abnormalities.

In most previous reports on the blood picture after splenectomy the emphasis has been laid on the changes in the red cells and hemoglobin, although far more striking changes, both quantitatively and qualitatively, have been recorded for the leukocytes. In the present case the anemia usually noted in man and in experimental animals was of such slight degree, if present at all, that attention was concentrated on the white cells almost exclusively.

In the nature of the case it was impossible to obtain a preliminary count that would represent the condition previous to the injury. After injury, but before operation, two counts showed respectively 25,250 and 15,250 white cells, with 83 per cent. neutrophils, 15 per cent. lymphocytes and 2 per cent. endothelial cells. As this was during the presence of free blood in the peritoneum, with consequent absorption of fibrin ferment and slight fever, these counts are best disregarded in the present study. At each examination a total and differential count of the leukocytes was made. For the latter a sufficient number of cells was counted each time to ensure satisfactory check results. This was usually 400 cells, but when the count ran unevenly or differed markedly from those preceding as many as 1000 cells were counted. The usual classification of cells has been adhered to, except that the large mononuclear and transitional cells have been placed in one group as endothelial cells.<sup>1</sup> During the

<sup>1</sup> McJunkin, F. A.: *Am. Jour. Anat.*, 1919, xxv, 27.

earlier part of the work the counts were made from films stained with Wright's stain, but as the fact became apparent that the endothelial cells were consistently increased, check stains were made with the alpha-naphthol stain of McJunkin.<sup>2</sup>

The counts were, as far as possible, taken at the same hour each day, from four to five hours after the comparatively light breakfast of the hospital wards.

In addition to the differential count the neutrophiles were classified according to Arneth's method. For facility in the comparison of results the sum of the numbers of cells in each hundred falling in groups 3, 4 and 5, that is, the more mature cells, is tabulated as the Arneth index.

The "normal" figures shown in the tables for comparison were obtained by averaging the figures given in five standard text-books. From these we conclude that the normal white count is one of 8000 cells, of which 5440, or 68 per cent., are polynuclear neutrophiles, 1920, or 24 per cent. lymphocytes, 400, or 5 per cent. endothelial cells, 200, or 2.5 per cent. eosinophiles, and 40, or 0.5 per cent. basophiles.

**THE RED CELLS.** The red cells have shown no notable change throughout. The slight reduction noted was perhaps not more than is accounted for by the hemorrhage found. A progressive increase in the red count was noted during the period of observation. The hemoglobin was recorded only in the later counts, as only then was a reliable instrument available. The final count showed 5,200,000 reds and 92 per cent. hemoglobin. Normoblasts were noted in two films, but not more than two were found in a specimen. No other abnormalities were seen. The fragility was not tested.

**THE WHITE CELLS.** A glance at the charts showing graphically the changes in the white blood cells (Charts I, II and III) impresses one at first with the irregularity and variability of the counts both total and differential. More careful study, however, shows that the observations may be divided into three periods: a first, comprising the first nine observations and covering the period from the seventh to the sixteenth day after the operation, a prolonged intermediate period, and a final period embodying ten observations extending from October 15 to November 5, at which time the study ended. The first and last periods show fairly consistently uniform results. The intermediate period is one of great irregularity and sudden change in the picture.

During the first period the total white count was consistently high, varying from 14,600 to 19,800, with an average of 17,000. The differential counts, too, as shown in Chart II, did not vary more than is to be expected in successive counts on a normal individual. The average differential for the period was: neutrophiles,

<sup>2</sup> Arch. Int. Med., 1918, xxii, 157.



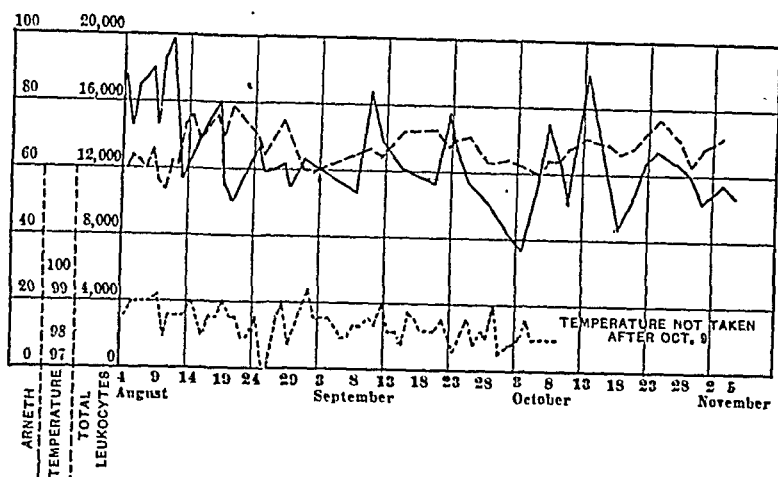


CHART I.—Total leukocyte count, Arneth index and temperature. Solid line, total leukocytes; broken line, Arneth index; dotted line, temperature.

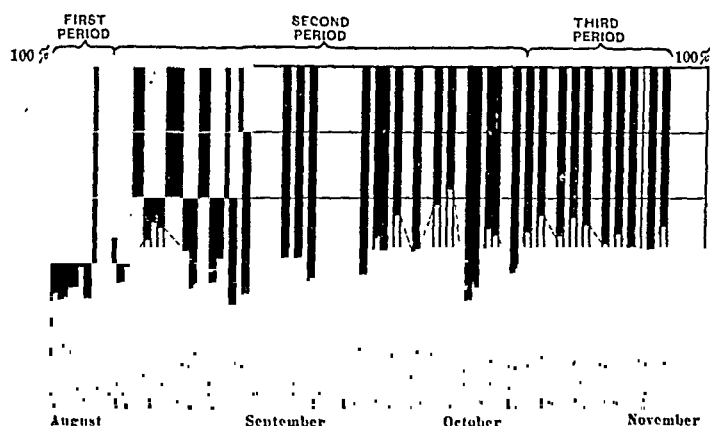


CHART II.—The differential count. Black, neutrophiles; white, lymphocytes; diagonal lines, endothelial cells; horizontal lines, eosinophiles and basophiles together.

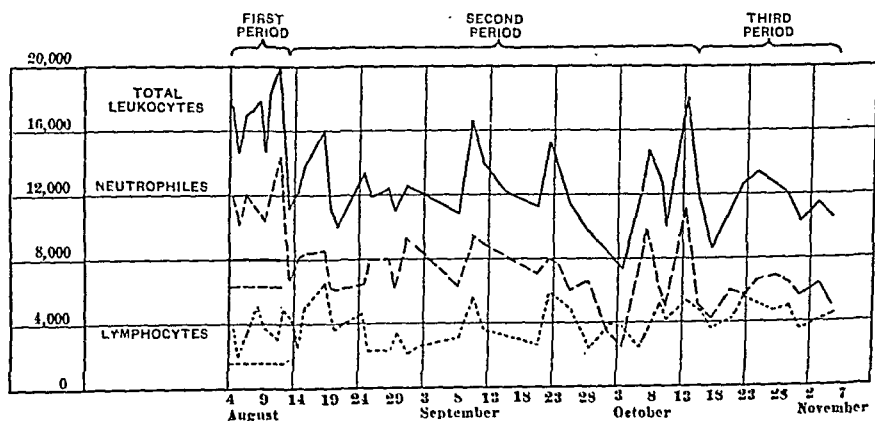


CHART III.—The actual numbers of neutrophiles and lymphocytes per cubic millimeter. Calculated from the total count and the percentage of each cell. Solid line, total leukocytes; broken line, neutrophiles; dotted line, lymphocytes. The short horizontal lines at the left end of the chart show the normal averages in each case.

68 per cent.; lymphocytes, 21.5 per cent.; endothelial cells, 8 per cent.; eosinophiles and basophiles together 2.5 per cent. With the exception, then, of a very small decrease in the lymphocyte percentage, with a corresponding increase in that of the endothelial cells, the differential relations are strictly normal, though the total count is more than twice the normal. Table II shows the number of each type of cell present and the ratio to normal in each case. The outstanding characteristic of this period would appear to be an increase to more than twice normal of the total number of leukocytes, with normal differential relations. During this period, too, the Arneth index approximated the normal.

The second period is characterized by such great variability that the computation of averages would be meaningless. The usual count was slightly above 12,000, but five times it went above 15,000, once reaching 18,000, and once for several days it fell to 8400 and 7400. The differential counts were equally bizarre. The neutrophile percentage varied between 72 and 37. Sometimes a sharp increase in total count was due to an influx of neutrophiles, but on at least two occasions (Chart III, August 18 and September 24) the rise was due mainly to a wave of lymphocytes. During this period the endothelial cells were consistently increased both relatively and absolutely.

In the third period the total count was still increased, but showed much more uniformity. The average was 11,570, or nearly once and a half the accepted normal. The extremes were 13,500 and 8700. The differential count showed still less variation than the total and is markedly changed from normal figures. The neutrophiles averaged 50.5 per cent., the lymphocytes 39.5 per cent., the endothelials, 7.8 per cent.; the eosinophiles and basophiles together, 2.2 per cent. Thus in spite of the increased total the actual number of neutrophiles present, as shown in Table II, and Chart III, is not above normal, and the increase in cells is due entirely to the mononuclear elements.

The average Arneth count on normal individuals, expressed in the way here used, is between 55 and 60. During the first period, then, the average index, 60.5, was not far from normal. With the beginning of the second period the index rose rather abruptly coincidently with a drop in the number of neutrophiles. According to the current conception of the cycle of development of the neutrophile this must mean a sudden cessation of production of this type of cell. However, subsequent increases in the number of neutrophiles were not accompanied by drops in the index, but rather the reverse obtained, a high point in the index tending to coincide with an increase in neutrophile count. During the concluding period the index remained well above normal, averaging 69. These relations are shown in Chart I.

TABLE I.—TABULATION OF BLOOD FINDINGS.

Date.	Red cells.	Hemo- globin.	Leuko- cytes.	Neutro- philes.	Lympho- cytes.	Endo- thelial.	Eosino- phile.	Mast cells.	Arneth index.
Aug. 4	4,320,000	....	17,500	69.0	20.0	7.0	4.0	0.0	60
5	....	....	14,600	71.0	13.5	14.0	2.0	0.5	64
6	....	....	17,000	70.5	15.0	12.5	4.0	0.0	62
7	4,370,000	....	17,300	67.0	20.0	6.0	5.0	0.0	59
8	....	....	17,900	61.0	33.0	5.0	1.0	0.0	66
9	....	....	14,800	70.0	24.0	3.0	2.0	1.0	57
10	....	....	18,600	....	....	....	....	....	54
11	4,460,000	....	19,800	73.0	16.0	10.0	0.0	1.0	62
12	....	....	15,500	63.0	31.0	6.0	0.0	0.0	61
13	....	....	11,200	52.0	39.0	8.0	1.0	0.0	73
14	....	....	12,300	66.0	20.0	12.0	0.0	2.0	76
15	....	....	13,700	61.0	37.0	0.0	0.0	2.0	67
18	4,650,000	....	16,000	53.0	41.0	4.0	1.0	1.0	76
19	....	....	11,000	47.5	47.0	4.5	0.0	1.0	70
20	....	....	10,200	49.0	38.0	11.0	1.5	0.5	79
24	....	....	13,300	56.0	35.0	9.0	0.0	0.0	70
25	4,460,000	....	11,900	67.0	29.0	12.0	1.0	0.0	64
28	....	....	12,300	65.0	28.0	4.0	3.0	0.0	74
29	....	....	10,900	58.0	34.0	5.0	1.5	1.5	69
31	....	....	12,600	72.0	18.0	9.0	0.0	1.0	60
Sept. 2	....	....	12,300	69.0	22.0	9.0	0.0	0.0	60
8	....	....	10,900	58.0	30.0	10.0	1.0	1.0	66
10	....	....	16,600	58.0	34.0	8.0	2.0	0.0	67
12	5,100,000	....	13,800	65.0	26.0	9.0	0.0	0.0	65
15	....	....	12,100	....	....	....	....	....	72
20	4,970,000	....	11,300	63.0	27.0	11.0	1.0	2.0	73
22	....	....	15,300	52.0	37.0	9.0	1.0	1.0	68
23	....	....	13,500	56.0	34.0	9.0	0.5	0.5	70
25	....	....	11,300	45.0	43.0	9.5	1.0	1.5	71
28	....	....	10,100	56.0	26.0	13.5	2.5	2.0	63
Oct. 1	4,930,000	....	8,400	42.0	46.0	9.0	1.0	2.0	64
3	....	....	7,400	37.0	52.0	8.0	1.0	2.0	63
6	....	....	12,000	70.5	22.5	4.5	2.0	0.5	60
7	....	....	14,800	66.5	22.5	9.5	0.5	1.0	64
9	....	....	12,800	49.0	40.0	8.0	2.0	1.0	64
10	....	....	10,200	50.0	40.0	8.0	2.0	0.0	67
13	....	....	18,000	62.0	29.0	7.5	0.5	0.0	71
15	4,600,000	90	12,000	51.0	39.0	7.0	1.5	0.5	69
17	....	....	8,700	45.5	43.0	9.0	2.0	0.5	66
20	....	....	11,000	51.5	37.0	10.0	1.5	0.0	68
22	....	....	12,600	45.5	45.0	7.0	2.0	0.5	....
24	5,200,000	90	13,500	48.0	40.0	9.5	1.5	1.0	77
27	....	....	12,700	54.0	37.5	8.0	0.5	0.0	71
29	5,200,000	92	12,000	51.0	40.0	8.0	0.5	0.5	63
31	....	....	10,300	55.0	35.0	6.5	2.0	1.5	68
Nov. 3	....	....	11,500	55.5	36.0	6.0	2.0	0.5	71
5	....	....	10,700	49.0	42.5	7.0	1.0	0.5	....

The effects of splenectomy in the dog have been exhaustively presented by Pearce, Krumbhaar and Frazier<sup>3</sup> in a recent monograph giving the results of their experimental work and a review of the literature of the subject. The removal of the dog's spleen produces constantly an immediate leukocytosis, mainly of the polynuclear variety, lasting for some months. There is relative

<sup>3</sup> The Spleen and Anemia, Clinical and Experimental Studies, Lippincott, Phila.

diminution of the lymphocytes and increase of the endothelial cells. In a majority of the dogs the eosinophiles were markedly affected, being largely increased either early or late in the course, and in some there was, for several weeks before the increase, a total absence of these cells.

TABLE II.

	Normal.	First period.		Third period.	
		Cells.	Ratio to normal.	Cells.	Ratio to normal.
Total leukocytes	8000	17,000	2.12	11,570	1.45
Neutrophiles .	5440	11,500	2.11	5,845	1.07
Lymphocytes .	1920	3,655	1.90	4,570	2.38
Endothelial cells	400	1,275	3.18	987	2.02
Eosinophiles .	240	510	2.12	255	1.06
Basophiles . }					

The actual number of each variety of leukocyte, and the relation of each to the normal.

TABLE III.

	Normal.	First period.	Third period.
Neutrophiles . . . . .	68.0	68.0	50.55
Lymphocytes . . . . .	24.0	21.5	39.50
Endothelial cells . . . . .	5.0	7.5	7.75
Eosinophiles . . . . .	2.5	2.5	1.5
Basophiles . . . . .	0.5	0.5	0.7

Comparison with normal of average differential counts of the first and last periods.

The recorded studies on the human are few and often conflicting. The reason for the discrepancies appears in the charts here shown, as from them it is easily possible to select a series of counts at fairly short intervals for a long period that would show almost any given picture with uniformity. The ideal case for this kind of work should show the removal of the organ for some small lesion that does not affect the structure or function of the mass of the organ, or for injury with only slight hemorrhage. For ideal conditions, too, a preliminary count should be made not only before operation but before injury in the latter class of cases. Moreover, as these figures clearly show, no conclusions can be safely drawn unless the counts are made at short intervals.

The cases that fulfil these requirements are very few indeed. Practically all reports show an immediate increase in the total white count, but the differential relations vary considerably. Some (Nicholas and Dumonhim,<sup>4</sup> and Meyer<sup>5</sup>) report lymphocytosis. Heaton<sup>6</sup> found a large increase in the large mononuclear and transitional forms. Musser<sup>7</sup> found the increase due mainly to polynuclear

<sup>4</sup> Jour. de physiol. et de path. gén., 1903, v, 1073.

<sup>5</sup> Jour. Am. Med. Assn., 1901, lii, 1231.

<sup>6</sup> British Med. Jour., 1911, lxxix, 501.

<sup>7</sup> AM. JOUR. MED. SC., 1911, cxlii, 501.

elements. Others (Nicholas and Dumonihim,<sup>8</sup> and Darling<sup>9</sup>) mention eosinophilia. Giffin<sup>10</sup> reports a case of splenomegaly in which the removal of the organ resulted in an enormous increase of eosinophiles, already numerous, and notes that these cells were of a more mature type than usual. The only reference to the Arneth index after splenectomy that I have been able to find referred to the condition after extirpation for pernicious anemia (Lee, Minot and Vincent<sup>11</sup>). In these cases the index, characteristically high in this disease (shifted to the right), returned toward normal.

In presenting these results it is recognized that the lack of a count before rupture detracts from their value. However, the subject had been in active military service as a cavalryman for over two years previously; his recovery was complete and the organ removed showed no abnormality other than the slight tear causing the bleeding. We seem justified in assuming the removal of a normal spleen from a normal man. The immediate effects of the operative procedure on the leukocytes should have passed when the counts were begun.

The results in this case may be summarized as follows: The moderate anemia present at the outset showed progressive improvement. The observations on the leukocytes may be divided into three periods: a first, characterized by a high count with all types of cell increased in practically normal proportion and a very slightly raised Arneth index; a second, showing great variability in total and differential counts and a varying but usually high Arneth; and a final period, in which the blood would appear to have attained to something approaching an equilibrium, and shows still some increase in the total count, but with the differential relations so altered that the increased total is seen to be due entirely to the presence of larger numbers of the lymphocytes and endothelial cells, while the granular leukocytes are present in normal numbers only. During this period the Arneth index remained consistently high.

It is perhaps permissible to suggest that the first period represents the effect on the organs of blood formation and destruction, of the removal of the spleen; the second period, lasting about two months, one of adjustment of the organism to the new conditions, while other tissues were possibly taking over the functions of the absent organ; and the final period one of comparative equilibrium, approaching the end point of the adjustment process. The immediate increase of all cells after operation suggests the removal of some factor that either restricts production of white cells or destroys those that have passed their usefulness. In the Arneth index we have for the neutrophiles a means of estimating which factor is mainly concerned. In the first period in this case the index was

<sup>8</sup> Jour. de physiol. et de path. gén., 1903, v, 1073.

<sup>9</sup> Med. Record, 1911, lxxix, 110.

<sup>10</sup> AM. JOUR. MED. SC., clviii, 158.

<sup>11</sup> Jour. Am. Med. Assn., 1916, lxxvii, 719.

very slightly increased. As the neutrophiles were present in more than double normal numbers it seems probable that the increase was not entirely due to lessened destruction. Moreover, the coincidence of a rise of the index with the first sharp drop of the neutrophiles at the beginning of the second period, the fact that during this period high points in the neutrophile curve tend to coincide with high points of the index, and that the index remained high with a normal number of neutrophiles in the final period, all suggest that the variations in the cell count are due at least in part to variations in the number of cells produced rather than to changes in the rate of destruction. This point of view would result in the conception of the normal spleen as exercising a restrictive action on the production of leukocytes.

**SUMMARY.** The results of these observations may be summarized as follows:

1. The removal of the spleen resulted in a considerable increase in the total leukocyte count which persisted with much irregularity for over three months.

2. In the early period all types of white cell were increased in nearly the same proportion, although a slight increase of endothelial cells was noted at the expense of the lymphocytes.

3. In the intermediate period both total and differential count showed such marked variation as to render averages valueless, but the total count usually was high.

4. In the final period a comparative equilibrium was reached, with a moderate increase in the total count, due entirely to lymphocytes and endothelial cells while the granular leukocytes showed strictly normal figures.

5. The endothelial cells were constantly increased both relatively and absolutely.

6. The observations on the Arneth index suggest that the increase in the count is at least in part due to the removal of some factor restricting the production of white cells.

7. No eosinophilia appeared during the course of the work.

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## MODERN INDIVIDUALIZED DIETARY TREATMENT IN DIABETES.

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**Historical Retrospect.** The basis of our dietary treatment of diabetes was created at the close of the eighteenth century by the English physician Rollo. The diet then was an animal mixed diet: 1.5 liters of milk, meat, fat and a little bread.

In the fourth decennium of the nineteenth century diabetic therapy began to show signs of individualizing. Bouchardat led the way, calling attention to the fact that milk in addition to animal diet poor in carbohydrates often disagrees with patients and that large rations of meat disagree with certain patients. In cases in which a little ordinary bread leads to glycosuria he used gluten bread or gave vegetables poor in carbohydrates and fruits.

In the seventies the absolute dietary forms flourished for a time. These were Cantani's absolute meat diet and the Englishman Donkin's absolute milk diet. Both writers thought they had found a therapy able to produce a lasting cure of the disease, provided only that the course of treatment were continued for long periods, the meat diet was to be kept from two to nine months and the milk diet no less than six weeks. Not until then might a cautious transition to a mixed form of diet be made. In the same period E. Külz made his researches into the influence of the different carbohydrates on glycosuria.

In the eighties an opposition arose to the strict meat diet as recommended especially by Cantani and Naunyn. It came from Ebstein, who had seen symptoms of threatening coma in a diabetic who had been put on a strict meat diet and in whose urine diacetic acid was shown to be present. Ebstein here originated a most essential individualization in the therapy of diabetes: in the cases in which the urine gives Gerhardt's reaction for diacetic acid a *sudden* exclusion of the carbohydrates of the food, which may greatly endanger the patient, should be avoided.

The use of the diet poor in carbohydrates in diabetes with acetone and diacetic acid in the urine was not, however, abandoned, even though there was a tendency, for some years, to abandon this form of diet in cases of moderate severity; for if only sudden elimination of carbohydrates was avoided, or, on Naunyn's advice, the urine was made alkaline by administering alkali (10 to 30 gm.) before starting strict diet, the threatening coma symptoms were avoided. If then a prolonged strict diet had spared the patient's weakened function, first the diaceturia and then the acetonuria were often seen to disappear.

Clinical experience showed, however, that there were severe cases in which the strict diet poor in carbohydrates did not bring about the disappearance of glycosuria. Already Cantani had in such cases used *short fasting*: keeping the patient fasting for twenty-four hours or longer, he left him without food and with only water or broth a few times a day from one day's evening to the forenoon of the third day. After disappearance of glycosuria Cantani returned to absolute meat diet, giving, however, only one-half or two-thirds of the ration formerly used, and not until fifteen to twenty days later was the meat ration increased. If sugar appeared, absolute fasting was reintroduced. Naunyn, too, used the fast day,

and Weintraud, his then collaborator, found by means of metabolic experiments that the diabetic after the fast day saved up considerable quantities of N.

In the nineties altogether a more *systematic quantitative individualization* of the diabetic diet set in. Weintraud at the Strassburg clinic and myself in Denmark at Frederiks Hospital experimented with methodic restriction of the content of protein of the diet, increasing at the same time the quantity of fat in cases of moderate severity. By means of metabolic tests Weintraud showed that a patient suffering from severe diabetes who had been rendered aglycosuric kept his body protein and weight when consuming a food corresponding to that of healthy individuals.<sup>1</sup>

In 1898 von Noorden replaced the fast day by the so-called *vegetable day*,<sup>2</sup> on which the patient got nothing but greens, butter, some fat pork, claret and one or two liqueur glasses of French brandy. The vegetable day has essentially the same action on glycosuria and ketonuria as the fast day; in my experience, however, often only if pork be excluded. Five years later von Noorden published the "oat-cure," which he, from 1907, greatly modified, giving, after a few days of strict diet, 1 or 2 vegetable days, then 2 or 3 oatmeal days and then again 1 or 2 vegetable days. If no aglycosuria was attained the whole rotation was repeated once or twice.

The oatmeal treatment proved particularly indicated in cases of moderate severity and severe cases with acidosis. In threatening coma oatmeal soup without butter was used *or* first 1 or 2 fast days (coffee, tea, mineral waters and 100 to 250 c.c. of French brandy or whisky), and when the greatest danger had passed, oatmeal gruel was prescribed.

L. Blum, of Strassburg, replaced oatmeal by *wheat flour*, with mainly the same result. Most practitioners, however, prefer oatmeal. But what was more important was that Blum taught us how to individualize with the quantities of oatmeal; advising in severe cases to use no more than from 150 down to 75 *grams*, by which means aglycosuria was more quickly attained.

*Vegetable diet poor in carbohydrates*, originally advocated by Kolisch and later by K. Petrén and myself, I now apply frequently in severe cases of diabetes with acidosis, as with this form of diet it is easier to administer small quantities of protein and a little more carbohydrate than it is possible to give in an animal mixed diet. Further, the alkaline reaction of this diet operates favorably in the presence of acidosis, and finally by this diet one is able to *reduce the total metabolism to the lowest point possible* and still satisfy the appetite of the patient and keep his weight. In fact, a low metabolism is

<sup>1</sup> Healthy people use: at rest, 30 to 35 calories; easy work, 35 to 40 calories; medium hard work, 40 to 50 calories.

<sup>2</sup> Or "green-day."



in certain severe cases, a life-and-death question. Only a consistently maintained *minimum diet* will succeed in keeping the percentage of blood sugar low (0.07 to 0.08 per cent.) and the urine free from sugar.

In my lecture given to the Medical Society of Copenhagen in 1912,<sup>3</sup> in which I demonstrated the favorable effect of a *vegetable diet poor in carbohydrates* ("mixed vegetable diet:" greens, eggs, pork, butter, tea, coffee, mineral waters, claret) in the case of diabetic acidosis, I also strongly pointed out that overfeeding the patients in diabetes was hurtful to them, and that a diet that just suffices to cover their requirement is what suits them best. The lives of patients are preserved the longest time in this way.<sup>4</sup>

In 1913 I discussed this question with Weintraud, who two or three times had pronounced in favor of "chronic undernutrition" in case of a severe diabetes.

**Experiments with Strict Vegetable Diet.** After this retrospect I pass on to the new experiments I have been making during recent years in my clinic.

First a number of experiments with a *strict vegetable diet* applied to both recent and older cases of diabetes. After the disappearance of glycosuria, hyperglycemia and acidosis, if any, a *slow* transition to a mixed diet poor in carbohydrate was made.

After twenty-four to forty-eight hours' observation on mixed food or on the diet prescribed by the practitioner sending him, the patient, in bed, was put on a strict vegetable diet, *i. e.*, 300 to 500 gm. of green vegetables (with 2 to 5 per cent. of carbohydrates), 60 to 75 gm. of butter, 200 gm. of bouillon, 150 gm. of cranberries, 1 egg, tea, coffee, soda-water and, sometimes, alcohol, such as claret, whisky or French brandy.

Vegetable diet was used from two to eight days until aglycosuria was attained and hyperglycemia had disappeared. (See tables I and II.)

In rather mild and fresh cases, glycosuria and hyperglycemia<sup>5</sup> disappeared on the first or second day, in cases of moderate severity and older cases from seven to eight days (see Table I) or even more may pass. If a mild *ketonuria* (acetonuria and diaceturia) is present

<sup>3</sup> Marius Lauritzen: *Diabetisk Acidose og dens Behandling* (Diabetic acidosis and its treatment), Nord Tidsskr. for Terapi, 1912; *Die Therapie der Gegenwart*, 1912.

<sup>4</sup> Weintraud wrote me on June 26, 1913 saying: "As to 'chronic undernutrition' and the value of it in treating severe cases of diabetes I have already several times stated my opinion. It is here, of course, not a question of a set form but of a test ('einen tastenden Versuch') of making the patients just keep their metabolic balance with the least supply of nutrition possible. The experience that to attain this end a less copious supply of nutrition than many are used to suffices, even in severe diabetes, contradicts the general opinion of many medical men that any diabetic has to eat more than the healthy individual, and I believe that our dietary treatments many a time are wrecked on this misconception that man has to eat such a lot. The great quantity is often nothing but a bad habit."

<sup>5</sup> In spite of high glycosuria pronounced hyperglycemia may often be absent in fresh cases. (Lauritzen.)

it may disappear quickly. In case of rather high degrees of acidosis it will, as a rule, be diminished, but may increase during the first twenty-four hours, especially if the N excretion in the urine is high and the butter ration is too abundant for the patient's acidosis.

TABLE I.—STRICT VEGETABLE DIET. H. N. P., THIRTY YEARS; MALE; DIABETES; ACIDOSIS.

Date.	Food.	Soda, gm.	Urine sugar, gm.	Blood sugar, %	Ammono- nia, gm.	N, gm.	Weight, kilos.
June 30	Mixed diet	10	123	0.14	2.4	10.6	63.2
July 1	1. Vegetable day <sup>6</sup>	20	30	....	2.5	10.8	
2	2. Vegetable day	20	21	....	1.68		
3	3. Vegetable day	20	22	....	1.2	5.8	
4	4. Vegetable day	20	12				
5	5. Vegetable day	20	traces	....	....	4.3	
6	6. Vegetable day	20	0	....	0.25	4.8	
7	7. Vegetable day <sup>7</sup>	20	0	0.07	0.25	4.0	63.2

TABLE II.—STRICT VEGETABLE DIET. E. K., FIVE YEARS; DIABETES.

Date.	Food.	Urine sugar, %	Urine sugar, gm.	Blood sugar, %	Ammono- nia, gm.	N, gm.	Weight, kilos.
May 3	Mixed diet	6.0	24	0.06	0.33	4.9	17.5
4	1. Vegetable day <sup>8</sup>	....	0	....	0.20	4.8	
5	2. Vegetable day	....	0	....	0.79	7.6	
6	3. Vegetable day	....	0	0.05	0.97	5.4	17.3
10	Mixed vegetable diet <sup>9</sup>	....	0	0.05	0.45	4.2	17.4
13	Mixed vegetable diet <sup>10</sup>	....	0	....	....	2.89	17.4
16	Mixed vegetable diet <sup>11</sup>	....	0	0.05	0.24	3.6	17.5

N in the urine falls from the prevailing level (13 to 18 gm.) to 5 to 8 gm. In children N in the urine is, as a rule, lower.

The body weight will often, to some extent decrease as much as 1 kilo or more; in other cases the weight remains almost unaltered.

The *transition* from strict vegetable diet to the diet that suits each patient is made slowly to avoid glycosuria, hyperglycemia

<sup>6</sup> Vegetables, 500 gm.; butter, 75 gm.; 1 egg; broth, 200 gm.; cranberries, 150 gm.; tea, coffee.

<sup>7</sup> Then patient passed on to "mixed vegetable diet" and at last roast meat, 50 gm. and cheese, 30 gm. were added. Uses no more soda. Remains sugar-free with normal blood sugar and has mild acetonuria. Is able to work.

<sup>8</sup> Vegetables, 300 gm.; butter, 60 gm.; 1 egg; cranberries, 75 gm.; soup, 200 gm.; tea.

<sup>9</sup> Vegetables, 200 gm.; butter, 60 gm.; 2 eggs; cranberries, 75 gm.; soup, 200 gm.; tea; boiled pork, 25 gm.; roast pork, 25 gm.

<sup>10</sup> + Aleuron bread, 50 gm.

<sup>11</sup> + Roast meat, 25 gm. Gets now mixed diet with gluten bread, 50 gm. (20 per cent. of carbohydrate). Is sugar-free, has normal blood sugar and mild acetonuria. Weight, 19 kilos.

and a sudden increase of acidosis if present. The glycemia is examined after each addition to the food. If hyperglycemia sets in a vegetable day is at once intercalated, thus often avoiding the occurrence of glycosuria, which I consider of great importance.

In *mild* cases the first additions to the vegetable diet are proteins: one or two eggs or 50 gm. of roast meat or of fish; next further additions of protein and fat, when the ration of vegetables may simultaneously be restricted to 300 to 400 gm.

In cases of *moderate severity* the first additions are fatty foods: 25 gm. of roast pork at a time, then boiled striped pork, eggs, fish and, at last, meat, always small additions. When acetonuria has disappeared the rations of vegetables are restricted to 300 gm., and fish and roast meat are increased to 150 gm. (to be weighed after preparation).

In *severe* cases, with rather strong acidosis, strict vegetable diet should be continued during several days, up to one week, and if this results in the elimination of glycosuria and in bettering acidosis, the patient gets small additions of roast pork, then of eggs and boiled pork and alcohol. If these additions are tolerated, fish, ham and meat are tried, but no more than 50 gm.

In strict vegetable diet I prescribe *alkalies* (sodium bicarbonate and citrate) as little as possible, these substances together with this diet easily causing retention of water and edema. Only in case the alkaline diet is unable by itself to keep the quantity of ammonia in the urine within normal limits, bicarbonate in doses of 5 gm. and upward, as suited to each case, may be given.

The advantage of *strict vegetable diet* over the gradual restriction of the carbohydrate and protein of the food is that aglycosuria and removal of hyperglycemia are *more quickly* attained, but in order to attain a result no less permanent and good than by gradual restriction the *transition* from vegetable diet to mixed diet poor in carbohydrates should be made quite slowly and according to the above-stated rules.

In the after-treatment *overfeeding should be avoided*, the patient getting the exact food rations that keep up his weight, and in young people and children the weight is to rise slowly, a quick increase of weight often causing glycosuria.

In cases of moderate or great severity large rations of protein should be avoided, especially protein of meat and casein.

I give in *mild* cases of diabetes from 1.5 to 2 gm. of protein per kilo of body weight; in *moderately* severe ones 1.0 to 1.5 gm. of protein per kilo of body weight; in *severe* cases 0.5 to 1.0 gm. protein per kilo of body weight.

It is difficult to fix precise caloric amounts for the food as a whole. It is necessary to individualize, trying by means of frequent weighings to find the right amount.

TABLE III.—P. H., SEVENTEEN YEARS; APPRENTICE; DIABETES OF MODERATE SEVERITY; ACIDOSIS.

Years, dates.	Pro-tein.	Fat.	Car-bohy-drate.	Urine sugar, %	Urine sugar, gm.	Blood sugar, %	Aceton-uria.	Diacet-uria.	Weight, kilos.
1911, Sept. 1 <sup>12</sup>	...	...	...	8.75					
1911, Sept. 21 <sup>13</sup>	...	...	...	5.0	100	.....	+	+	50.4
1911, Oct. 20	98	181	24 <sup>14</sup>	....	0	.....	+	÷	51.0
1912, Jan. 3	98	181	24	....	0	.....	+	÷	54.0
1913, Jan. 1	134	220	52 <sup>15</sup>	....	0	.....	+	÷	54.0
1913, Oct. 27	134	220	52	....	0	.....	÷	÷	56.0
1914, Mar. 31	123	223	58 <sup>16</sup>	....	0		+	÷	
1914, Apr. 18	123	223	58	....	0	0.083	+	÷	54.0
1915, Apr. 10	123	223	58	....	0	0.085	+	÷	56.0
1916, Sept. 6	123	223	58	....	0	.....	÷	÷	56.0

TABLE IV.—OATMEAL TREATMENT AND PROLONGED MIXED VEGETABLE DIET. F. P., THIRTEEN YEARS; BOY; DIABETES OF MODERATE SEVERITY; ACIDOSIS.

Date.	Food.	gm. soda.	% urine sugar.	gm. urine sugar.	% blood sugar.	Diacet-uria.	gm. ammo-nia.	gm. N.	Weight, kilos.
1915, Jan. 18	Mixed diet	..	8.0	80	0.15	+	....	....	28.8
19	1. Vegetable day	..	6.0	60	....	++			
20	2. Vegetable day	..	3.0	23	....	++			
21	1. Oatmeal day <sup>17</sup>	..	1.25	25	....	÷			
22	2. Oatmeal day	..	1.0	22	....	÷			
23	1. Vegetable day	..	0.5	8	....	÷	....	....	28.9
24	2. Vegetable day	..	0.25	4	....	÷			
25	3. Vegetable day	..	....	trace	....	+			
26	Oatmeal day	..	0.25	6	....	÷			
27	1. Vegetable day	..	....	0	....	+	....	3.07	28.4
Feb. 1	Mixed vegetable diet <sup>18</sup>	2½	....	0	....	÷	....	....	29.1
1916, Aug. 22	Mixed vegetable diet	2½	....	0	0.07	+	1.29	4.2	35.0

When a diabetic has been freed from glycosuria and acetonuria or has but a weak acetonuria left, the *minimum* will most frequently be 30 calories per kilo and sometimes less. If the patient performs light work from 35 to 40 calories; if heavier work above 40 calories will most frequently be the proper allowance.

In very young persons and children the amount of calories per kilo is *higher*. The following are examples:

<sup>12</sup> Mixed food.

<sup>13</sup> Diet with gluten bread from September 2.

<sup>14</sup> About 2200 calories. Carbohydrates in greens and compotes (light work).

<sup>15</sup> About 2800 calories. Carbohydrates in greens and compotes; gluten bread (heavier work).

<sup>16</sup> About 2800 calories. Carbohydrates in greens and compotes; gluten bread.

<sup>17</sup> Oatmeal, 75 gm.; butter, tea, 60 gm.

<sup>18</sup> Vegetable, 500 gm.; butter, 75 gm.; 2 eggs; pork, 100 gm.; soup, 200 gm.; cranberries, 150 gm. = 36 gm. of protein, 160 gm. of fat, 169 gm. of carbohydrate = 1753.

A male, aged seventeen years, with diabetes of moderate severity, used in his seventeenth and eighteenth years from 43 to 41 calories per kilo at *light work*, in his nineteenth to twenty-second years about 53 calories at *heavy work*. (See Table III.)

A boy, aged thirteen years, used in his thirteenth and fourteenth years 1750 calories or from 58 to 50 calories per kilo. His weight rose from 29 to 35 kilos. (See Table IV.)

**Experiments with Prolonged Fasting.** In a number of cases I have used prolonged fasting as recommended by Frederick M. Allen.<sup>19</sup>

On the basis of experiments made by him with fasting and then scanty feeding in diabetic dogs after partial pancreatectomy, Allen proposed to try similar prolonged fasting in diabetes in man, using after the fast small food rations that prevented any important increase of weight, glycosuria and, as far as feasible, acetonuria.

Allen's method of treatment is as follows:

1. *Fast days* (patient only gets coffee up to seven times daily, and, contingently, whisky in rather large doses, sometimes some 200 gm. and, in the case of considerable acidosis, sodium bicarbonate). Fasting is to be continued until the disappearance of glycosuria and preferably one or two days longer.

2. The day after fasting from 200 to 300 gm. of greens low in carbohydrates are given, which are increased from day to day, until reappearance of a little sugar in the urine. Then again one fast day.

3. After this *protein* is given. On the first day 1 or 2 eggs, then more protein in the form of eggs and meat, until the urine contains a little sugar. Then another fast day.

4. At last fats are given in gradually increasing quantities.

With patients that cannot be kept aglycosuric on low-class vegetables (with 4 or 5 per cent. of carbohydrate) these vegetables are boiled a few times and the water is strained off.

In patients made aglycosuric, Allen now and then saw mild glycosuria appearing after somewhat plentiful addition of fat, and in such cases he takes care not to give large fat rations.

At the Hospital of the Rockefeller Institute, Allen tried the treatment of prolonged fasting in 100 cases, and he thinks that aglycosuria was attained more quickly than by means of gradual restriction of carbohydrates and protein. Allen urges that after fast days the supply of food should not increase too quickly and that the patient's loss of weight during fasting should not cause alarm. Altogether, Allen is of opinion that a reduction of weight is in itself beneficial to the diabetic and serves to spare the weakened function and increase tolerance.

The treatment with prolonged fasting was tried in 8 cases by L. M.

<sup>19</sup> Allen, F. M.: The treatment of diabetes, Boston Med. and Surg. Jour., February, 1915. Prolonged Fasting in Diabetes, AM. JOUR. MED. SC., October, 1915. Allen, Stillman and Fitz: Rockefeller Institute Monograph, No. 11, 1919.

Hill and I. L. Sherrick<sup>20</sup> (Boston). They praise the method, proceeding, however, in a somewhat different way: After fast days until aglycosuria was attained they gave one vegetable day with 15 gm. of carbohydrate and then one day a diet containing 15 gm. of carbohydrate, 25 gm. of protein and 150 gm. of fat. After this they gradually increased fat, then protein and, at last, carbohydrate. Of fat they did not give more than 200 gm., and the amount of calories rarely exceeded 2200 per day.

Elliot P. Joslin,<sup>21</sup> too, has used Allen's prolonged fasting treatment following his indications. After fasting, however, he gives only 150 gm. of vegetables, then fruit poor in carbohydrate, then protein, and finally fat until the patient ceases losing weight.

In the cases in which I have tried prolonged fasting it was not always as easy to carry through the treatment as with the strict vegetable diet, some few patients objecting, others being psychically affected in a less fortunate way by the fast which, surely, has the drawback of being rather severe.

The following are a few instances of the fasting treatment (Tables V and VI):

*Table V.*—Female, aged thirty-five years, suffering from *adipositas*, *mild* diabetes and gangrene in crus. She had had diabetes for several years, and shortly before entering the clinic she had 7 per cent. of sugar; no albuminuria or acetonuria. On entering she had a gangrenous ulcer the size of a palm on left crus. After the third fast day the urine was sugar free and hyperglycemia had disappeared. *Now acetonuria and diaceturia appeared*, remaining during the following vegetable days without entirely disappearing, until mixed diet with 20 gm. of gluten bread and 300 gm. of greens was begun. On this diet she remained free from glycosuria and hyperglycemia. The *gangrenous ulcer* healed entirely. Patient is constantly sugar free. She now gets 100 gm. of gluten bread (with 20 per cent. of carbohydrate) per day.

*Table VI.*—Female, aged thirty years, with *severe* diabetes and acidosis. Patient had been suffering from diabetes a year, and had for several months been free from glycosuria and hyperglycemia, with mild acetonuria. Some weeks before entering the clinic glycosuria and hyperglycemia had set in again owing to a faulty diet. On the second fast day the urine became sugar free and remained so (except on September 26) during slow transition to mixed vegetable diet, which she still keeps. The table shows how the percentage of blood sugar becomes normal.

*During fasting acetonuria and diaceturia behave differently* (see tables), according to whether the cases of diabetes under treatment are mild or severe. In *mild* diabetes acetonuria and diaceturia

<sup>20</sup> Boston Med. and Surg. Jour., 1915, p. 696.

<sup>21</sup> AM. JOUR. MED. SC., 1915, p. 485.

appear on the second or third fast days, continuing on the following vegetable days, but disappearing on transition to mixed diet with more carbohydrate. In *severe* diabetes with acidosis the latter decreases, i. e., acetonuria and diaceturia abate and the quantity of ammonia in the urine diminishes. On the following vegetable days the quantity of ammonia increases again, owing to a sudden supply of nourishment (fat and protein). It is a well-known fact that in the case of severe diabetes metabolism of fat from the food increases acidosis more than metabolism of fat from the organs. After a few days of vegetable diet the quantity of ammonia again becomes normal.

TABLE V.—FASTING TREATMENT. A. H., FIFTY-FIVE YEARS; FEMALE; MILD DIABETES; GANGRENE.

Date.	Food.	Sugar, %	Sugar, gm.	Blood sugar, %	Diacet- uria.	Ammo- nia, gm.	N, gm.
July 4	Mixed diet	7.0	70	....	÷		
Aug. 5	Diet with 100 gm. gluten bread	1.0	12	0.17	÷		
9	1. Fast day	...	traces	....	÷	....	6.24
10	2. Fast day	...	traces	....	÷	0.52	6.94
11	3. Fast day	...	0	0.07	++	0.75	5.92
12	Vegetable day	...	0	....	++	1.6	9.09
13	Vegetable day	...	0	....	++	1.2	5.96
14	Mixed diet <sup>22</sup>	...	0	....	+	1.12	5.40
16	Mixed diet <sup>23</sup>	...	0	0.08	÷	0.7	

TABLE VI.—FASTING TREATMENT. A. P., THIRTY YEARS; FEMALE; SEVERE DIABETES; ACIDOSIS.

Date.	Food.	Sugar, gm.	Blood sugar, %	Ammo- nia, gm.	N, gm.	Weight, kilos.
Sept. 22	Diet with 30 gm. gluten bread	21	0.155	1.61	8.69	50.2
23	1. Fast day	13	....	0.43	5.90	49.2
24	2. Fast day	0	....	0.51	5.72	48.2
25	Vegetable diet <sup>24</sup>	0	....	2.0	6.92	48.6
26	Mixed vegetable diet <sup>25</sup>	traces	0.096	0.99	6.66	48.6
27	Mixed vegetable diet <sup>26</sup>	traces	....	0.93	5.32	48.6
28	Mixed vegetable diet <sup>27</sup>	0	....	1.7	5.33	49.2
29	Mixed vegetable diet <sup>28</sup>	0	0.075	1.05	5.29	49.2
30	Mixed vegetable diet <sup>29</sup>	0	....	0.68	4.86	49.3

<sup>22</sup> Roast meat, 50 gm.; pork, 59 gm.; 1 egg; butter, 60 gm.; vegetables, 300 gm.; cranberries, 150 gm.; one-third bottle of claret, tea, coffee.

<sup>23</sup> + Gluten bread, 30 gm.

<sup>24</sup> Vegetables, 400 gm.; butter, 60 gm.; soup, 200 gm.; cranberries, 150 gm.; tea, coffee, 30 gm.; French brandy.

<sup>25</sup> + 1 egg and roast pork, 25 gm.

<sup>26</sup> + 1 egg and roast pork, 25 gm.

<sup>27</sup> + Boiled pork, 25 gm.

<sup>28</sup> + Roast pork, 25 gm. and butter, 15 gm.

<sup>29</sup> + Roast meat or fish, 50 gm.

The excretion of N in the urine depends, of course, on the supply of protein on the days preceding the fast days.

(In *healthy individuals* the quantity of N in the urine is rarely, in case of fasting, less than 10 gm. On the second day, and often not until the third or fourth days, N in the urine *rises*, an occurrence which probably is due to the fact that the stock of glycogen of the body diminishes and, on the third day, is exhausted. After this rise the metabolism of protein *decreases* slowly during continued hunger. During the first ten days it rarely sinks under 10 gm.).

The same state of things as in healthy persons I found in diabetics on fast-days. That the N figures in these two cases were lower was due, no doubt, to the patients being beforehand on a food poor in protein. On the first vegetable day after fasting N rises in the urine, but it soon decreases again on mixed vegetable diet. (I met with the same state of things in my experiments with *strict vegetable diet*. See Tables I and II.)

**The Modern Individualized Diabetic Diet in Practice.** It follows from what is stated above that diabetic therapy has been developing more and more toward individualizing dietary treatment.

This was bound to be the case, the closer study of diabetes showing doctors the diversity of the disease: first the mild functional troubles that remain mild for years without dietary treatment of any importance, then other mild cases that owing to complication with other diseases demand a thorough change of the ordinary diet, and then other mild cases that, now suddenly now gradually reveal themselves as severe diabetes. Finally there are the cases of moderate severity with ketonuria, which may be expected soon to grow severe; they are changed by strict treatment into mild ones, the urine remaining normal for years.

It is evident that a single dietary scheme does not suit these different forms and stages of the disease. Each patient has to be carefully examined and be treated with the diet that qualitatively and quantitatively suits him at the time. Not only the content of carbohydrate of the diet, but also the rations of protein and fat should be empirically fixed according to the stage of the disease.

Some old and modern methods of treatment, such as absolute milk diet, oatmeal treatment, the strict vegetable treatment and fasting, proved of importance as passing short treatments in certain fixed cases and under dangerous situations, and they are of great use to us when applied with good judgment and prudence.

The forms of diets used during long periods, such as "animal diet poor in carbohydrate" and "mixed vegetable diet," are tolerated by many patients for years. If dyspepsia, which may be preliminary to threatening coma, appears, the great point is to break off in time, giving various small rations of carbohydrates or prescribing fasting or oatmeal gruel diets. After disappearance of dyspepsia the diet poor in carbohydrate may be prudently resumed, when a period



again sets in during which the patient may for months or years be kept free from glycosuria and acetonuria or with a slight acetonuria. At last in *severe* diabetes a time will come when the effort of keeping the patient aglycosuric by means of the above strict forms of diet will fail, and at the same time as glycosuria increases acidosis will gain strength. Then, before all, it should be tried to better the patient's function by one of the above-mentioned methods of treatment: strict vegetable treatment, oatmeal treatment or prolonged fasting. If these attempts fail, there is nothing left but prescribing a mixed diet somewhat richer in carbohydrate. This will increase the patient's glycosuria sometimes slowly, in other cases more quickly. In the former case acidosis will remain moderate, but if glycosuria increases quickly, acidosis will gain strength too, sometimes in a higher degree than glycosuria.

I shall now describe the *dietary treatment* of diabetes as carried on at present in my clinic, of course in its broad features only.

Complication with other diseases may, as a matter of course, influence the dietary treatment. So such cases will be mentioned by themselves.

**Fresh Uncomplicated Cases of Diabetes** manifest themselves as *mild* cases or as *cases of moderate severity*. (It is very rare to observe a fresh case that from the very beginning is severe. It is nearly always possible through anamnesis to show that the disease has been in existence a short or long time previously without being discovered.)

In the presence of an apparently *mild diabetes* I give the patient for a day or two mixed food or the diet prescribed by the practitioner who sent him to the clinic. At the same time blood sugar, urinary sugar, N and ammonia in the urine of the last twenty-four hours, which is also tested for acetone, diacetic acid, albumin, etc., are quantitatively determined. Then diets are prescribed as follows:

1. *Test diet* for two or three days. The test consists of 150 gm. of roast meat, 4 eggs, 80 gm. of butter, 50 gm. of cheese, 300 gm. of vegetables (with 2 to 5 per cent. of carbohydrate), 100 gm. of compote of rhubarb, 200 gm. of broth, 100 gm. of cream, 100 gm. of bread, one-third bottle of claret, 500 gm. of tea, 500 gm. of coffee, 500 gm. of soda water. This diet contains 104 gm. of protein, 140 gm. of fat, 72 gm. of carbohydrate, 18 gm. of alcohol = 2151 calories. In some mild cases the urine will be sugar-free in two or three days. If this is not the case, or if the percentage of blood sugar remains above the normal on such food, that is, 0.08 to 0.09 per cent., then

2. *Vegetable diet* (see above) is prescribed for one day, when

3. *Animal diet* as in the test diet is prescribed, but without cream, bread being, according to the nature of the case, replaced by 60 to 120 gm. of gluten bread or left out altogether, or changed for vegetables very poor in carbohydrates. The rations of gluten bread or vegetables which are tolerated without developing hyperglycemia after the meal are prescribed.

The diet fixed in this way is kept for *months*, often for a *couple of years*, before further additional carbohydrates are admitted, and is constantly controlled by blood analyses. *Milk* is never prescribed in uncomplicated cases, nor *cream* either, only exceptionally 50 to 100 gm. of "whipping" cream.<sup>30</sup> Now and then it occurs that the patient, after a couple of years, is able to pass on to ordinary mixed diet (with no sugar in it) without developing glycosuria.

In mild cases, too, which, when following their normal course, pass off without any lasting acetonuria and diaceturia, the diet poor in carbohydrate may be seen to develop ketonuria at the beginning of the treatment. The ketonuria, however, disappears little by little as carbohydrate tolerance improves, and may often be got rid of by increasing the protein of the food, protein in this case acting on acetonuria in the same way as addition of carbohydrate (as in healthy individuals) in contrast with what is seen in severe cases when additional protein is apt to increase acidosis.

In *uncomplicated cases of apparently moderate severity* or when a case that to begin with was considered a mild one proves to be of moderate severity, that is one in which the above test-diet less bread, cream, cheese, wine and butter (kneaded in water) to which vegetables very poor in carbohydrates are added, is unable to remove hyperglycemia and glycosuria, various methods may be made use of:

1. The treatment described above, with *strict vegetable diet* for several days, may be applied until the attainment of the desired result, when a *slow* passage to mixed diet poorer in proteins than the first diet is made.

2. Instead of strict vegetable diet *fasting* may be used as advised by Cantani or Allen, followed by a *slow* passage to a diet poor in protein.

3. One may rest content with intercalating *one vegetable day at a time* and then pass to a diet poorer in protein intercalating, if needed, another vegetable day, after which the ration of protein is further restricted, until blood sugar and urine are normal. If the case is one apt to develop ketonuria, as in children and very young people, I generally have recourse to

4. Von Noorden's "oat cure" with the rations of oatmeal and butter (kneaded in water to remove fatty acids) that are suited to each individual case; after the concluding vegetable days I *slowly* pass to strict animal diet with vegetables.

(N. B.—If the patient is not in hospital or clinic, and if one does not fully master the technic of vegetable treatment, fasting treatment or "oat cure," method No. 3 should be chosen as being *harmless*, easily carried through and productive of results that are equal to what is attained by means of the other methods, as long as it is a diabetes of moderate severity).

<sup>30</sup> First-class cream used for whipped cream.

If the presence of diaceturia should in any way trouble the practitioner then, besides the vegetable days intercalated, which effect a lowering of acidosis, small doses of *alkalies* may be used, increasing from 5 gm. per day until the urine is alkaline.<sup>31</sup>

Diabetes of moderate severity which is not treated or not treated with sufficient energy and length of time with small food rations preventing hyperglycemia and glycosuria will more or less quickly pass into the last stages of the disease. We shall then be face to face with the *severe* and *severest* cases in which *diabetic acidosis* has such great influence on the treatment.

In *severe cases* of diabetes with *acidosis of moderate severity* in which the quantity per day of ammonia in the urine is from 2 to 3 gm. (on mixed antidiabetic diet with some 30 gm. of carbohydrate) it should always be tried by means of energetic treatment to change the case from a severe one into a moderate one, a plan which will often prove a success.

In my clinic we observe the patient a couple of days on the diet he follows at the time, determining daily ammonia, urinary sugar and N in the urine. The pulse is daily examined in view of acidosis. Analysis of blood sugar is made at least twice a week. If the patient uses soda he continues the same dose. He is out of bed resting two or three hours daily.

As a rule, *treatment* (3) (see above) is now applied with reduction of the protein of the food, especially meat and food containing casein (cream, cheese, milk).<sup>32</sup> Thus both protein and carbohydrate are gradually restricted, being replaced by green vegetables until the attainment of aglycosuria and the lowest percentage of blood sugar possible, best of all 0.05 or 0.06 per cent. If for some reason or other, *quick* attainment of sugar-freedom is wanted, *vegetable treatment* (1) or *fasting* (2) with confinement to bed are used, being continued until the object is attained. In case aglycosuria and hypoglycemia are not attained by treatment (3), acidosis being heavier than usual, I try von Noorden's *oatmeal treatment*.

If one of the above treatments proves successful in rendering urine and blood normal and removing ketonuria, *diet poor in protein + vegetables poor in carbohydrates with washed-out butter* or with olive oil, vinegar and other spices, and for drinks, soda water, tea, coffee, aquavitæ or French brandy, should be continued as long as possible. The patient's life may then be preserved for years. If dyspepsia sets in the treatment is broken off, the diet being modified or one or two days' fasting prescribed.

In the *severest cases with heavy acidosis*, when there are 4 to 8 gm. of ammonia in twenty-four hours (on mixed diet with about 30 gm.

<sup>31</sup> The first days of alkali therapy may cause an increase of acetonuria and diaceturia, but the addition of alkali should be continued, until the urine is alkaline.

<sup>32</sup> My experience is that in these cases, too, these proteins are less well tolerated than vegetable protein.

of carbohydrate) the treatment is attended with greater difficulties. Here we, as a rule, also have *obstipation* and *dyspepsia* to contend with.

*Confinement to bed* for a more or less extended period is necessary. The degree of acidosis will somewhat diminish through *vegetable treatment* or *fasting* with or without subsequent *oatmeal treatment*. Also *alkalies* should be used to obtain alkaline urine. Though glycosuria may not be quite removed, it may often be lowered to from 10 to 20 gm. in twenty-four hours, and ammonia to 0.5 or 1 gm.

The diet of the *after-treatment* must contain *very small quantities* of *proteins*, especially vegetable protein and protein of hen's eggs, which are better tolerated here than any other. The carbohydrate of the food must be derived from vegetables and fruits containing little carbohydrate; if required, small rations of bread are given. Milk and cream had better be avoided, both milk sugar and casein affecting glycosuria unfavorably, but should at times be conceded to give a variety to food. Of *fats*, vegetable fat, butter (kneaded in water) and pork are given, but all in rather small rations on account of acidosis, which at this stage is rather sensitive to fats. *Alcohol*, on the contrary, acts favorably, being almost indispensable and full of advantages. Patients tolerate large doses of it; it does not increase glycosuria and has a good effect on acidosis. Good claret, hock, sugar-free champagne, French brandy, whisky, aqua vitæ are given according to the patient's liking.

If small helpings (25 to 50 gm.) of roast meat or fish agree without a great increase of glycosuria or acidosis, they give a good variety to diet.

**Coma Diabeticum Incipiens.** In acute exacerbation of acidosis, which is preliminary to coma, we see the precomatose symptoms: increased thirst, troubled sleep, headache, rapid pulse and respiration with deep inspirations. An energetic and consistent treatment at this first stage of coma nearly always takes the patient over the serious situation; but at the somnolent stage, too, one often succeeds in bringing about a lasting cure. On the contrary, in the case of deep coma I have never obtained more than a brief restoration to consciousness by means of *intravenous injections* of a 3 per cent. solution of sodium bicarbonate (solution sterilized in a not hermetically closed flask over the fire for ten minutes). From 25 to 30 gm. sodium bicarbonate are injected.

In the *first stage* of coma incipiens: confinement to bed, absolute quiet, surveillance by a trained nurse and the doctor the few hours during which there is any hope of saving patient. The latter is kept warm. Every quarter of an hour he gets a teaspoonful of sodium bicarbonate well stirred in water; camphorated oil frequently injected subcutaneously and, in case of specially weak action of the heart, digalen (1 c.c. intravenously) or strophanthin, Boehringer ( $\frac{1}{2}$  to 1 mg. intravenously). If no *quick* improvement sets in, with

the pulse becoming less rapid and respiration normal, the treatment with soda every quarter of an hour and heart tonics is continued. As soon as the state has improved the intestine is evacuated without making any tax upon patient (decoction of senna and enema of 3 parts of water + 1 part of glycerine, if any). Directly after defecation camphorated oil is administered subcutaneously.

**Diet.** Formerly absolute milk diet was used and, after the introduction of the "oat cure," only oatmeal gruel made of 100 to 150 gm. of oatmeal without butter, hot or cold with lemon, especially with emaciated patients that are thought not to have taken any excess of nourishment immediately before coma. But otherwise, for twenty-four to forty-eight hours, I use no food but alcohol (French brandy, whisky) diluted with water, and then oatmeal gruel diet for one or two days. If then the patient has an appetite, further 150 gm. of vegetables with 20 gm. of butter are given and, for dinner, broth with vegetables. The passage to mixed vegetable diet with restriction of the oatmeal ration is slow, and the dosage of soda required to keep the twenty-four-hour urine alkaline is provided. Confinement to bed continues at least four weeks after incipient coma is well over.

**Diabetic Therapy in Children.** 1. In infants in the first or second years of life the course is rapid, and in no case did I succeed in improving function to any essential degree. After water diet I passed to milk mixture or oatmeal gruel, or mixed vegetable diet.

2. In older children in whom *glycosuria* is found I give, after a strict vegetable diet, an animal diet poor in carbohydrates and then with caution gluten bread or aleuron bread to the extent tolerated without developing hyperglycemia and glycosuria.

A child, aged five years, weight 18 kilos, received 2 eggs, 60 gm. of pork, 60 gm. of butter, 25 gm. of roast meat or fish, 150 gm. of green vegetables, 45 gm. of gluten bread and 75 gm. of cranberries. The urine remained sugar-free; blood sugar 0.06 per cent.; slight acetonuria and N 4 to 5 gm. in twenty-four hours. The child has one vegetable day and then one day without bread per week.

Diet must be continued for two years before more carbohydrates are allowed and only with control of blood sugar.

In cases of mild glycosuria cure was sometimes obtained through prolonged strict diet. In cases of *moderate severity* and in *severe* cases an energetic treatment may greatly better prognosis *quoad durationem vitæ*, but sooner or later coma will occur. Here I use confinement to bed and after removal of hyperglycemia and glycosuria by means of one of the 4 above stated treatments I pass to mixed vegetable diet continuing keeping it as long as there is a possibility of carrying it through.

**Example:** Boy, aged thirteen years, suffering from diabetes mellitus and acidosis. Admitted on January 18, 1915. Diabetes began

December, 1914. There was 8 per cent. of sugar in 1000 c.c. of urine; acetonuria and diaceturia. After vegetable treatment combined with oatmeal treatment urine and blood were rendered normal. Slight acetonuria continued.

In 1915 the patient was on 100 gm. of pork, 2 eggs, 200 gm. of broth, 500 gm. of vegetables, 75 gm. of butter and 150 gm. of cranberries and rhubarb = 36 gm. of protein, 160 gm. of fat, 28 gm. of carbohydrates = 1753 calories. Body weight oscillating between 29 and 34 kilos.

In 1916-1919 same diet as in 1915. Urine: sugar, 0; blood sugar, 0.07; slight diaceturia, about 1 gm. of ammonia, N, 3 to 4 gm. Body weight, 35 kilos.

The boy is quite well and able-bodied at his home, a small place in the country.

Children that are more spoiled will, as a rule, require a greater variety of diet.

**Diabetes Complicated with other Diseases.** It would take us too far afield to speak of the treatments used in all the complicated organic diseases met with in diabetes, but some of the most important must here be included.

*Diabetes with Diseases of the Kidneys.* In the case of *albuminuria* appearing and disappearing without other signs of chronic nephritis, care should be taken not to give too large rations of meat and eggs and to avoid concentrated spirits and sharp spices.

*Chronic nephritis* in diabetes calls for greater changes of diet. If in a diabetic *acute exacerbation* occurs in nephritis, for instance on a diet too rich in protein,<sup>33</sup> I use, in my clinic, *absolute milk diet* (1500 c.c. of milk or partly buttermilk, 250 c.c. of water or no water). Then glycosuria will often disappear, the retention of sodium chloride be removed and edemas, if any, disappear. General health improves. Then passage to mixed diet with gradual restriction of milk and addition of vegetables, fruit, butter, some roast meat or fish. At last the diet will be, for instance: 50 gm. of roast meat or fish, 1 egg, 100 gm. of unsalted butter, 200 gm. of vegetables, 50 gm. of unsalted bread, 500 gm. of milk, 250 gm. of cream, and 200 gm. of fruit (= 50 gm. of protein, 160 gm. of fat, 80 gm. of carbohydrate = 2066 calories).

In certain cases of moderate severity doing away with milk and cream altogether will be attempted, giving more vegetables and compote and 125 gm. of "whipping" cream thinned with water. Daily quantity of liquid 1500 to 2000 c.c. Of spices: vinegar, lemon, some vanilla. Of alcoholic drinks: 1 glass of mild claret or Moselle with water.

*Diabetes with Diseases of the Vascular System and Heart.* *Arteriosclerosis* is widespread among fat and elderly diabetics. It is met

<sup>33</sup> Or in the case of acute infection.

with only rarely in young individuals suffering from severe diabetes. There is good reason to use moderate rations of eggs and meat, prescribing plenty of vegetables, also bread and, if need be, milk, no more, however, than will keep down glycosuria.

Attacks of cardiac asthma or angina pectoris or tendency to asystole indicate<sup>34</sup> absolute milk diet, as stated above, for a short time (and then passage to mixed diet). Absolute milk diet, in connection with confinement to bed, is of use, too, in the case of *valvular defects* with failing compensation. Also when *circulatory disturbances in the liver* or *chronic hepatitis* exist, milk diet may periodically be used with advantage.

*In diabetes with chronic disease of the pancreas in which intestinal utilization of protein and fat is defective* treatment with *pancreon*, 5 or 6 gm. daily, which is a great aid to absorption, is used for years with intervals of a few weeks. In mild cases *diet* is as usual. In cases of moderate severity it is not always easy to find the proper diet. By way of example: a man, aged forty-eight years, received, after removal of glycosuria and acetonuria, 150 gm. of roast meat, 50 gm. of pork, 4 eggs, 50 gm. of cheese, 100 gm. of butter, 300 to 400 gm. of vegetables, 100 gm. of cranberries and rhubarb;  $\frac{1}{2}$  bottle of claret and two small glasses of aqua vitæ. He used 5 or 6 gm. of *pancreon* per day with intervals of a few weeks.

*Diabetes and Tuberculosis of the Lungs.* According to my experiences the patient should go through a regular antidiabetic treatment in hospital so as to remove glycosuria and hyperglycemia. If this result is successfully maintained for months, it acts favorably on tuberculosis of the lungs. After this the patient may, if desired, be sent to a sanatorium for tuberculosis of the lungs, adhering to the diet required. In case of severe acidosis and prognosis pessima, the patient as far as possible should stay at his home.

*Diabetes and Acute Febrile Diseases.* In severe infections diet is to consist of liquid food, whereas in milder diseases one may, as a rule, be content with modifying the diet used at the time.

In *acute pneumonia* in a *mild* diabetes the prescription of the first days is: 1 liter of cooled milk and  $\frac{1}{2}$  liter of lemon-juice in water with saccharine, 1 cup of broth. If at night the thirst is very intense, then three or four times 100 c.c. of lemon-juice with water. The following days, until the crisis comes, care is taken to increase gradually the quantity of food:  $1\frac{1}{2}$  liters of milk and  $\frac{1}{2}$  liter of cream, the latter to be thinned with water and kept in a cool place. The heart is stimulated by 60 c.c. of fine French brandy and  $\frac{1}{4}$  liter of dry sherry. After the crisis the same food is given a few days, when the mixed diet formerly used is gradually resumed.

<sup>34</sup> In these cases I also obtained a capital effect by using fasting for some days and then reduced vegetable diet.

In cases of *moderate severity* with acidosis I use oatmeal gruel diet suited to each special case, and alcohol in large doses. When there is no more fever one vegetable day is intercalated, and, by a frequent use of vegetable days, reintroduction of the diet poor in carbohydrate is attempted.

In *influenza* with a high fever and *typhoid fever* diet is essentially as stated above, only in the latter case solid food is not to be given until at least a week after the fever has entirely ceased.

In *diabetes* complicated with *adipositas* and *gout* due regard should, of course, be had, in diet, to these diseases. The same thing holds good of diabetics suffering from *diseases of the stomach and intestine*, *diseases of the skin*, *morbus Basedowii* and *nervous diseases*. Thus, whereas fasting may be suitable in diseases of the stomach and intestine, it cannot be used in Basedow's disease or with highly nervous diabetics.

As to *syphilitic* diabetics I always submit them to an antiluetic treatment at the same time as diabetic treatment is carried through.

In *diabetic gangrene* it is of great importance to remove hyperglycemia as quickly as possible. Here I use *strict vegetable* diet or *fasting* according to the state of the patient. Blood sugar is frequently examined.

Before *operating* on diabetics glycosuria and hyperglycemia should, as far as possible, be removed. In case of acidosis the urine must be made alkaline by vegetable diet, if need be by alkalies, and should be kept slightly alkaline for some time after operation until all danger of threatening coma seems passed.

Finally a few words on *prophylaxis in diabetes*.

1. In families in whom diabetes occurs the doctor should now and then test the children for glycosuria, particularly after acute febrile diseases, in furunculosis or in case of other symptoms indicative of hyperglycemia, eventually prescribing a starchy meal and examining the urine passed after the lapse of four hours. In diabetic families it stands to reason that the doctor directs parents as to the children's mode of life so as to avoid a food too rich in carbohydrates.

2. In life-insurance examinations, in polyclinics and hospitals, when a reduction is found in the urine of a patient, an examination after a test-meal should be made in doubtful cases. Diabetes may thus often be discovered in its incipient stage.



ROENTGEN-RAY STUDIES OF BRONCHIAL FUNCTION.<sup>1</sup>

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SEVERAL clinical problems, among them the accumulation of abundant bronchial secretion in laryngeal diphtheria and the formation of bronchiectases and antra, seem to depend upon a more correct understanding of the processes by which the lungs evacuate themselves.

Fluoroscopic observations and studies of the radiographs of an injected tracheobronchial tree in a patient suffering from a malignant tracheo-esophageal fistula seemed to disclose what we interpreted as the evidence of a peristaltic action in the bronchi. Another case, Beeler's,<sup>2</sup> has been reported, but the reduced reproduction of the bronchi does not lend itself to interpretation of detail. Both our own case and that of Beeler died as the result of lung supuration.

This is not remarkable in view of the fact that infected fluids were injected and in both cases, it is believed that the fistula interfered with the proper emptying of the lung.

Rosenberg, in 1887, was the first to inject the bronchi therapeutically. Chevalier Jackson reported the insufflation of bismuth powder and recommended its utilization in diagnosis. The experiments of C. A. Waters, S. Bayne-Jones<sup>3</sup> and L. G. Rowntree were performed to study the anatomy of the bronchial tree and record the use of thorium and iodoform and bismuth pastes. Some of the dogs in which iodoform was used died.

Our first experiment was with a fox terrier bitch, 20 c.c. of thorium nitrate in sodium citrate solution being injected into the bronchial tree through a catheter. In spite of the prompt evacuation of the thorium solution, by posture, the animal experienced marked dyspnea, rapid irregular heart action and died about fifteen minutes later. A slide of this lung showed that the thorium had already penetrated the pulmonary vessels by osmosis. In another dog, which died from chloroform anesthesia, the excised lungs were filled with thorium solution and radiographed. The radiogram was unsatisfactory because the solution spread beyond the confines of the bronchial tree, invading the parenchyma.

<sup>1</sup> Read before the Section on Medicine, New York Academy of Medicine, November 18, 1919.

<sup>2</sup> Jour. Am. Med. Assn., vol. xlv, p. 178.

<sup>3</sup> Arch. Int. Med., April 16, 1917, p. 538.

A second dog injected with a small quantity of thorium survived until the following morning. When the lungs at postmortem were injected with barium in acacia they showed details of lung structure



FIG. 1.—No. 8. October 16, 1919. Black and white fox terrier, five and a half minutes after injection of 1 mil. of adrenalin chloride. Dog had received 10 c.c. of barium in olive oil suspension. The terminal bronchi are contracted.

as far as the alveoli and served to visualize the conception of lung structure very much as do corrosion specimens.

The lungs of a fourth dog were injected with barium in gelatin

after chloroform anesthesia, using the formula employed by Louis Gross in his injections of the vascular trees of excised organs. This experiment gave pictures which were too indefinite for satisfactory study, and the dog so injected died of a pneumonia involving the area injected six days later. This was attributed to a decomposition of the gelatin.



FIG. 2.—No. 9. October 18, 1919. Black and white fox terrier after injection of adrenalin, in deep inspiration.

It was now decided to employ a medium which would not putrefy and which could readily carry a larger amount of barium. It was felt that iodoform poisoning had probably contributed to the death of the dogs in the Waters, Bayne-Jones and Rowntree experiments. Barium sulphate was triturated with anhydrous olive oil until a thick, smooth paste was formed. This paste was injected into anesthetized dogs directly into a bronchus in amounts of 5 to 10 c.c., depending upon the size of the dog. In one dog barium was tri-

turated with liquid petrolatum to form a thick paste. This was as satisfactory as the olive oil, and more readily sterilized. Only one of the dogs has died. Our dogs have been reinjected at an interval of three to seven days. In one dog the experiment was repeated twice in the same evening, when it was found that the lung had emptied itself after an hour. So far in our experiments the procedure

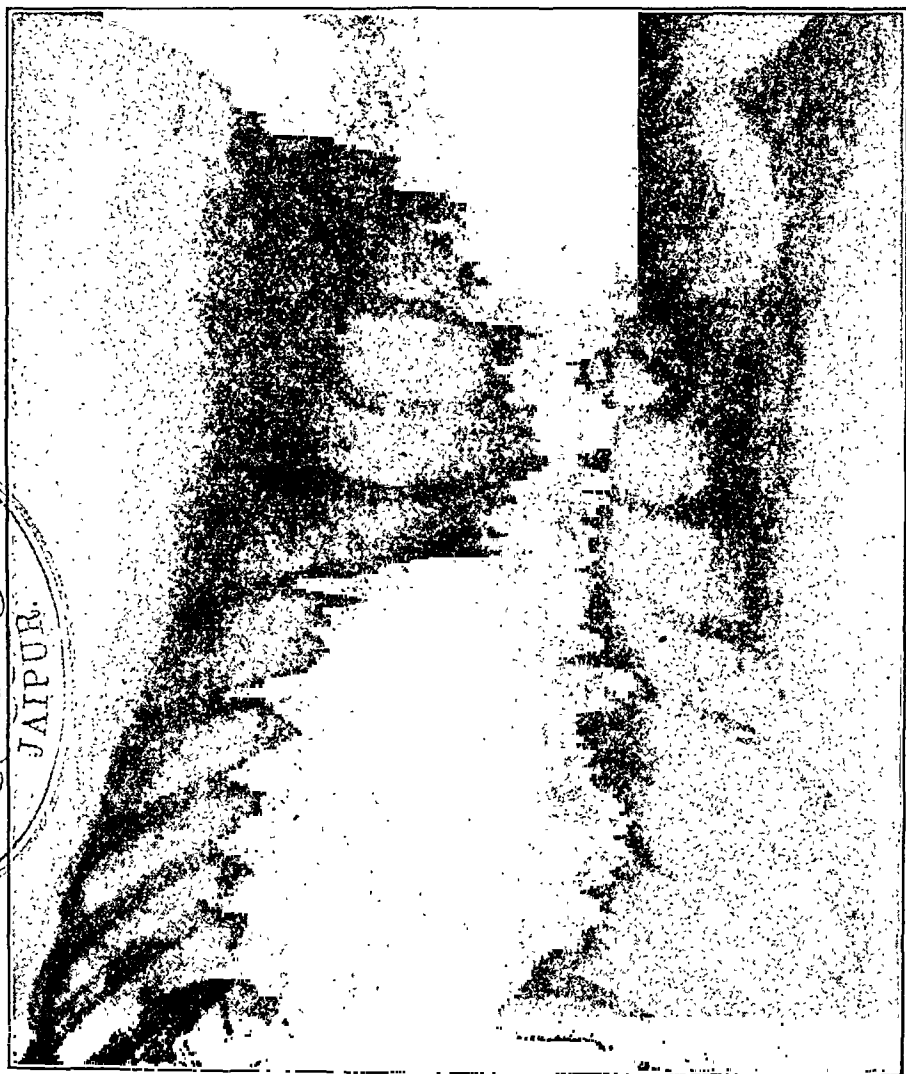


FIG. 3.—No. 10. October 18, 1919. Black and white fox terrier after injection of adrenalin, deep expiration. Note that ribs are elevated and bronchi are narrow in contrast to appearance in No. 9.

seems relatively innocuous in healthy dogs. One small dog which was injected with a large amount of barium in oil, retained sufficient in the right lower lobe to cast a shadow, which radiographically simulated a pneumonia for several weeks. After four subsequent injections the dog wasted away and finally died. A roentgen ray

of the lung shows a general filling of the alveoli with barium. The external surface of the lung appeared white in places.

The dogs were studied fluoroscopically and radiographs were taken. Most of the dogs tolerated these injections excellently.

Under the fluoroscope we have studied the movements in the bronchi and have observed the following phenomena:



FIG. 4.—No. 15. October 28, 1919. Male brindle pup anesthetized with ether, 10 minims of adrenalin chloride; five minutes later, 5 c.c. of barium in oil, which went into the stomach; ten minutes later, 10 minims of adrenalin chloride; then tracheal injection of 10 c.c. of barium in oil; immediate plate. Terminal bronchi are spastic so that barium may not enter.

1. If the left diaphragmatic bronchus and its branches are injected it is seen to move laterally with each pulsation of the heart.

2. There is, synchronous with respiration, a bellows-like expansion and contraction of the trachea and bronchi, which is very obvious in the relaxed bronchus immediately after injection, and especially if the anesthetic has not completely worn off (Figs. 2 and 3).

This expansion and compression of the bronchi is probably produced by costal breathing and the suppression of this bellows-like

action when movements of the ribs are limited may have deleterious effects. It seems possible to infer, from our observations, that the spastic contraction of the bronchus is as important in limiting the expansibility of the lung as it is in diminishing the caliber of the bronchi. Observations on chronic stenosis of the larynx at the Willard\_Parker Hospital by one of us (J. G. M. B.) have established

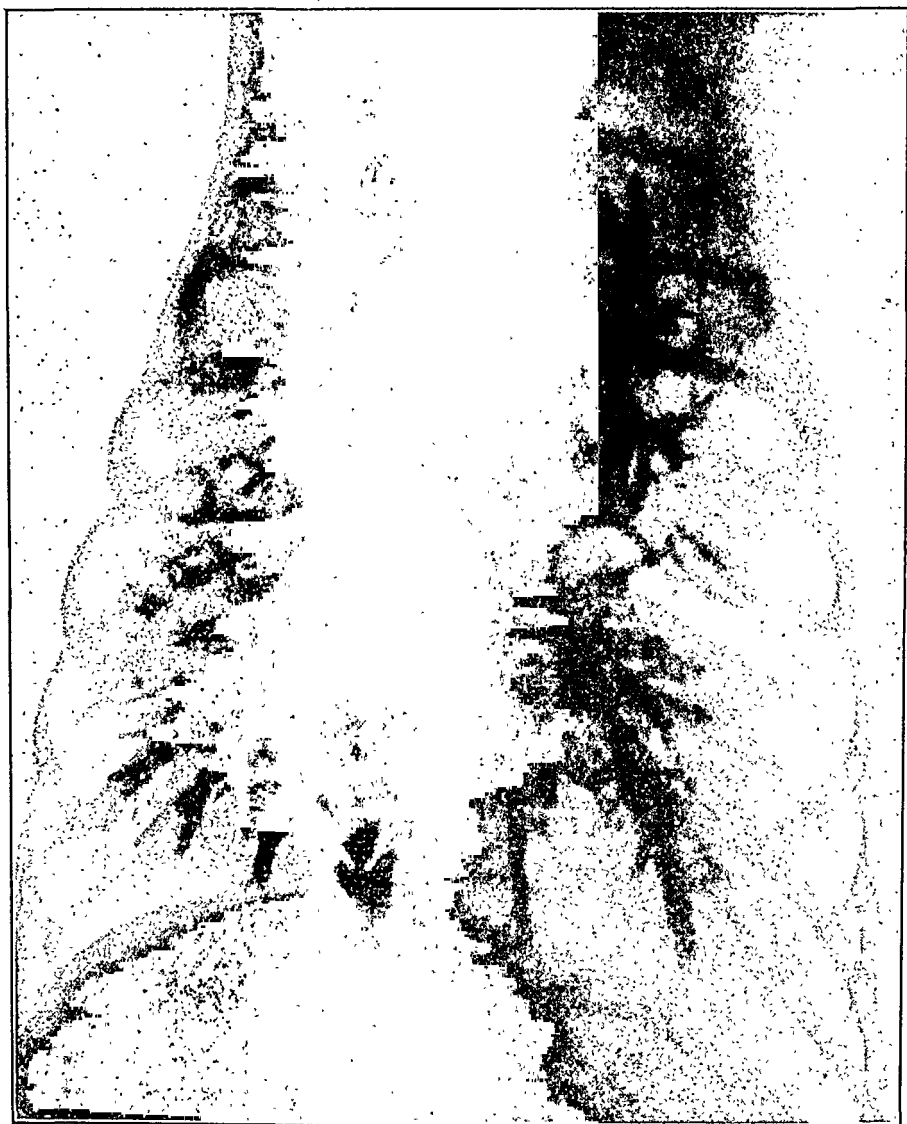


FIG. 5.—No. 16. October 28, 1919. Adrenalin given before tracheal instillation of barium. Terminal bronchi contracted and not filled.

the fact that a reduction in the tracheal lumen to one-third its size does not interfere with adequate respiration. Our observations may prove important in explaining the pathology of bronchiectasis and

recall von Basch's views on the importance of lost distensibility in the production of asthma and emphysema.

3. In addition to the two movements of the bronchus mentioned a third movement of larger cycle was observed. This is a movement



FIG. 6.—No. 18. October 28, 1919. Peristaltic movement of trachea and bronchi; lateral view.

of long peristaltic wave (10 cm.), though its amplitude is small. It is visible immediately after the injection of barium, and seems to be a potent factor in the evacuation of the bronchi and trachea. It is readily seen if a given point in the bronchus is kept under observation, at this point the bronchus or trachea is seen to contract and dilate



FIG. 7.—October 28, 1919. Same conditions on very rapid plates demonstrating peristaltic wave in trachea and bronchi; anterior view.



slowly, independent of cough, respiration and swallowing. It travels up the bronchial tree. This movement seems to us to account for the wave-like structure observed in the human bronchus injected with barium in acacia and also to be revealed in the dogs injected with barium paste, and may be contrasted with the sac-like character of the excised injected bronchi.

We submit a plate (Fig. 7), taken with great speed, which reveals sharply this peristaltic wave. We regret there is no available method of radiographic cinemetography, so that these movements may be analyzed more accurately. The lungs seem to empty themselves largely by means of this peristaltic movement, for even when the dogs are held upright so that gravity which readily empties a dog's lung cannot act, successive masses of the injection are seen to be expelled from the larynx and to travel down the esophagus without evidence of accompanying cough. This movement is entirely too rapid to be attributed to ciliary action.

4. We have also studied bechic movement under the fluoroscope. Under their influence the chest and abdominal muscles contract simultaneously, so that the lung and bronchial branches are crowded toward the trachea. These branches are shortened and crowded together.

It is probable that the air contained in the alveoli is expired in a more concentrated blast. Under the influence of cough the bronchi are emptied more rapidly. It is possible that contraction of the bronchial muscles directly influences by traction or nervous stimulation the contraction of the chest parietes.

We injected adrenalin in dogs after filling their bronchi with barium and hoped to see the bronchi dilated. To our surprise the bronchi appeared smaller. Notwithstanding the fact that when pictures were taken, the same phase of respiration was obtained, as shown by the position of the ribs. This observation is not in accord with that accepted as the physiological action of adrenalin on bronchial muscles. At first it was thought that the lung had emptied itself in the interval allowed for the adrenalin to act. In order to avoid this confusing factor, adrenalin was administered to a dog before the barium was injected. We obtained the same result. In one dog adrenalin caused an increased rate of emptying of the bronchus with coughing. In another dog after giving benzylbenzoate, which is alleged and was observed to cause bronchial dilatation, adrenalin was given and the bronchi were found to be contracted. In another dog bronchial spasm was induced by administering 1 mg. of muscarin intravenously. This was associated with considerable coughing and persistent general muscular twitching. An intravenous dose of adrenalin relaxed the spasm of the bronchi and caused the twitching to disappear. (See illustrations.)

We are aware of the shortcomings and paucity of our observations, but we have concluded to report them, with the conviction

that the observations contribute to a more correct understanding of the physiology of the bronchi.

In conclusion we have observed:

1. A bellows-like action in the trachea and bronchi which may be limited by contraction of the bronchial muscles.
2. A peristaltic action of the bronchial muscles, which seems adequate to empty them without invoking ciliary movement.
3. The action of adrenalin, benzyl benzoate, ether and muscarin have been observed by this roentgen-ray method.

The writers wish to record their debt to Dr. William B. Giles and Dr. Louis Griessman for valuable assistance and collaboration.

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## HETEROPLASTIC BONE FORMATION IN THE FALLOPIAN TUBE.

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IN the course of a routine examination of tissues recently removed at operations on the gynecological service of the Barnes Hospital, my curiosity was aroused by the difficulty which I encountered in attempting to cut a block of tissues from a Fallopian tube. Upon a closer inspection what appeared to be a spicule of bone, about 5 mm. wide and less than 1 mm. thick, was seen to protrude from the cut end of the tubal lumen. There were several other foci of similar resistance in the wall of the tube and in the mesosalpinx.

**Presentation of the Case.** The patient, M. J., a negress, aged thirty-seven years, was admitted to the gynecological service of the Barnes Hospital with complaints of a pain in the left lower quadrant and a firm mass in the lower abdomen. The family and past histories were unimportant. Menstruation started at the age of thirteen, and has been always regular, recurring every twenty-eight days and lasting from seven to twelve days. The flow has been rather profuse as a rule. The patient has not missed any period except in connection with her pregnancies. She has had intermenstrual bleedings for the past three years. The last menstrual period started on August 24, 1919 and was still continuing at the time of admission, September 14. The patient has had three pregnancies, two of which were full term and one a miscarriage. The oldest child is twenty years old and the miscarriage occurred ten years ago. The present illness dates back for three years, with an aching pain in the left lower quadrant. The pain was constant, and on several occasions during

the past three years the patient was compelled to take to bed for two or three days at a time. The hard lump in the lower abdomen was noticed only two months ago. General physical examination showed a fairly well-nourished colored woman in good health. Abdominal and pelvic examination revealed a spherical tumor mass which occupied the pelvis and the lower part of the abdomen, and was connected with the uterus. A diagnosis of uterine myoma was made and a laparotomy was performed by Dr. H. S. Crossen on September 18, 1919. At the operation the following notes were made:

"Mid-abdominal incision. Uterus is enlarged to the size of a grape-fruit, with fibroids. Both tubes are enlarged and distended with fluid. The left ovary appears normal. The right ovary is enlarged and chronically inflamed. Many adhesions are seen around the adnexa. The supravaginal portion of the uterus, both tubes and the right ovary removed. There is a calcified nodule of the size of a bean in the ovary."

The specimen was brought to the Laboratory, September 18, 1919, and was numbered, Gynecological Pathological No. 1288.

*Gross Description of the Specimen.* The formalin fixed specimen consists of the oval-shaped, supravaginal portion of the uterus, the left tube and the right tube and ovary. The uterus measures 13 x 11 x 8 cm. It is roughly of the size and shape of a grapefruit. It is covered on its surface with shaggy, loose fibrous tissue, which is grayish white in color. On cutting it open the dilated uterine canal is seen to contain a dark, grayish mass, measuring 8 cm. in its longest diameter. It is shaped like an alligator pear, with its superior and inferior axis elongated. The mass tapers gradually toward the lower end of the uterine canal; it is soft and pliable in consistency and it is attached to the uterine wall by means of a thin, fibrous band.

Both tubes are dilated and tortuous. The left tube measures 8 cm. in length. In its proximal third the organ retains its normal size and appearances. In the distal two-thirds it is dilated into a cyst-like sac whose greatest diameter is 3 cm. Its wall is as thin as parchment, it is semitransparent and it sends off several septa, thus converting the interior of the sac into several separate chambers. The contained fluid is colorless and watery.

Many loose fibrous adhesions pass between the right tube and ovary. The ovary measures 4 x 3 x 2.5 cm. The tube measures 7 cm. long, 1.5 cm. in transverse diameter close to the uterine cornua and 1.2 cm. throughout the rest of its length. In the mesosalpinx close to the tube there is a point at which the cutting knife meets with a considerable resistance. Similar resistance is encountered in the entire length of the tube except close to the uterine cornua. On the cut surface the tubal lumen shows a spicule of bone about 5 mm. wide and less than 1 mm. thick, firmly embedded in the substance

of the tube. The wall of the tube and the mesosalpinx also contain many small bony areas. The ovarian tissues do not seem to contain any trace of bone-like material. The ovary and the tube were cut together into several blocks about 1 cm. thick, decalcified in phloroglucin and nitric acid, embedded in celloidin, several sections being cut from each block.

*Microscopic Description.* The uterine tumor proved to be a myoma which has undergone hyaline degeneration in many places. The left tube was chronically inflamed. The right ovary appeared normal except for a chronic perioöphoritis, and showed no calcified or ossified areas.



FIG. 1.—A section of the entire tube and a portion of the ovary is shown. The ovary appears normal. In the mesosalpinx, in the upper portion of the section, there are several black streaks and dots which represent bony and cartilaginous islands. Calcium deposits that are located in this region are not visible. In the wall of the tube (lower portion of the section) there are several similar streaks. In the lumen of the tube will be seen a less deeply stained bony bar surrounded by hyaline connective tissue.

In the mesosalpinx between the right tube and ovary there are several foci of intense lymphocytic infiltration. In this same area the bloodvessels also are numerous and are distended with blood. In the small area midway between the ovary and tube there are several points at which the connective tissue is somewhat denser than elsewhere, and it is in these connective-tissue areas that the bony spicules occur. Close to some of these bony spicules are also seen some islands of cartilage (Fig. 1).

One of these cartilaginous islands which is included between two parallel rows of bone has certain peculiarities. On one of its sides there is a slender bar of bone having a somewhat serrated outline and containing in its substance much minute, deep blue: staining material resembling closely the cartilaginous tissue. Along its outer borders are a small number of osteoblasts. On the opposite side of the cartilage there are three separate bars of bone, each somewhat more slender than the one just described and much shorter (Fig. 2). These bony bars are separated from one another by somewhat hyaline connective tissue which contains scant, fusiform nuclei. The cartilage enclosed between these rows of bones is composed of



FIG. 2.—Numerous islets of cartilage are apparently undergoing destruction, and are surrounded by connective tissue. A fraction of bone is shown on either side of this cartilage. These bones contain deeply stained remnants of cartilage.

numerous minute islets of pale blue staining, irregularly outlined tissue, which contains here and there cells resembling plasma cells. These cartilaginous islands are of various sizes and appear decidedly porous, as the result of the presence of numerous variously sized cavities in their substance. Some of these cavities are apparently closed cavities and others mere indentations along the border. In these cavities and indentations there is often seen reticular connective tissue containing many clear vacuoles which resemble fat spaces. It also contains capillaries filled with erythrocytes and lymphocytes. The connective tissue in these indentations is continuous with that lying without, and contains a moderate number of capillary

vessels. The indentations above mentioned are decidedly angular in shape and thus give the impression that the cartilage might be in the process of destruction. The fibrous connective-tissue cells in this region and in the indentations are slender and contain moderately numerous, slender, fusiform nuclei, and appear rather young. In this neighborhood, where erythrocytes are found in a great number, apparently free in the connective tissue whose cells appear to be young fibroblasts in the process of organization, there are seen several foci of calcific deposits. These deposits are in the form of minute rings which surround a mass of erythrocytes in some instances and a hyaline mass of what appears to be fibrous tissue in other instances. In still other instances they consist of solid, spherical masses. These evidently represent a calcification of small vessels and capillaries which have undergone a hyaline thrombosis. Some of the larger deposits show under a higher magnification cells which possess radial processes, very much like bone corpuscles. Osteoblastic cells are not readily made out in connection with these calcific deposits, except in some few instances.

Other cartilaginous islands are also closely associated with osseous tissue and show deposits of calcium salts which on section appear as deeply blue-stained granules. At this calcified area the cartilage cells have lost their outline entirely and are converted into a single area surrounded by ossified tissue. Around these ossifying cartilages erythrocytes are found in a large mass as if a hemorrhage may have occurred. The connective tissue on the whole is hyaline here. A definite lymphocytic infiltration is also noted (Fig. 3).

In this area one also meets with a few gland-like structures lined by a low cuboidal epithelium. Immediately beneath this epithelium are found some lymphocytes. Some minute ossified nodules impinge upon the epithelium from underneath and at some points push it out into the gland-like lumen. Some of these nodules are definitely associated with cartilage, others evidently independent, but both are surrounded by lymphocytes and osteoblasts.

The wall of the tube contains numerous foci of ossification which are more or less continuous with the area above described, no definite line of demarcation being visible. These foci differ very little from the description given above.

The mucosa of the tube presents an almost normal appearance except that the submucous connective tissue contains numerous capillaries which are filled with a large number of polymorphonuclear leukocytes, both neutrophilic and eosinophilic. This connective tissue is also infiltrated with lymphocytes and appears definitely hyaline. There are a few foci of ossification in the submucous connective tissue. These bone spicules also contain in their substance deeply blue-stained material.

The continuity of the mucosa of the tube is interrupted at two opposite poles of its lumen by a rather broad band of tissues con-



FIG. 3.—Cartilage is undergoing ossification. Swollen cartilage cells, granular calcium deposits and new-formed bone are to be seen.



FIG. 4.—One of the bony bars found in the tubal lumen is shown. There are two typical Haversian systems.

taining two spicules of bone (Fig. 1). The lining on either side of this band is directly continuous with the epithelium of the tubal mucosa, and is composed of flattened cells. The band shows a well-formed bony bar which contains a moderate number of healthy corpuscles and a few typical Haversian canals. This bone is also covered with a few osteoblasts. Immediately outside of this osteoblastic membrane the connective tissue is loose and contains a number of fat vacuoles. Another bar of bone is arranged almost in a parallel direction to the one just described. This bone is located close to the tubal mucosa and is considerably smaller than the other. These two rows of bone enclose between them thick layers of connective tissue which contain delicate, fusiform nuclei, lymphocytes and fat vacuoles (Fig. 4).

Between the larger bone spicule and the lining of the "band" there are thick layers of hyaline tissue the elements of which consist of long, parallel, fiber-like structures which are very poor in nuclei and thus qualify for the so-called osteoid tissue (Fig. 1). Intimately mixed with this osteoid tissue are a few minute pieces of bone surrounded by a few osteoblast-like cells. Toward the portion of the mucosa where its continuity is broken by the band of tissues above described the connective tissue appears more like normal except for lymphocytic infiltration.

In short, the Fallopian tube presents a picture of a definite chronic inflammation of its fibromuscular wall and the mesosalpinx, in which are several foci of cartilaginous tissue undergoing a degeneration both alone and accompanied by ossification. There are in the mesosalpinx, close to the tube, definite evidences of calcific deposition which has involved arterioles and capillaries that have undergone a hyaline thrombosis. Cartilage is here seen to be in an actual process of ossification, in which process the area ahead of ossification is a seat of deposition of granular calcium salts and of the disappearance of the outline of the cartilage cells. Thus swollen and irregular cartilage cells are seen lying within the ossifying cartilage, a part of which has been calcified. The bone found in this case varies from a well-formed one with typical Haversian systems of a sort of marrow spaces to an incompletely developed bar still containing remnants of cartilaginous tissue. The bone, in addition to its association with degenerating cartilage, is seen to lie free in the osteoid tissue independent of either cartilage or calcific deposit. Such a bone, however, contains in its substance what has been described as the remnants of cartilaginous tissue.

**Discussion.** Numerous cases of aberrant bone production have been recorded in the literature. The majority of these cases have occurred in the cardiovascular system in connection with sclerosis and calcareous degeneration. Howse,<sup>1</sup> Marchand,<sup>2</sup> Paul,<sup>3</sup> Rosen-

<sup>1</sup> Tr. Path. Soc., London, 1877, vol. i.

<sup>2</sup> Eulenberg's Real-Encyklopaedic, 1885.

<sup>3</sup> British Med. Jour., 1885, vol. xxviii.



stein,<sup>4</sup> Kryloff,<sup>5</sup> Schroetter,<sup>6</sup> Roehmer,<sup>7</sup> Moenckeberg,<sup>8</sup> Thorel,<sup>9</sup> Bunting,<sup>10</sup> Harvey,<sup>11</sup> and Buerger and Oppenheimer<sup>12</sup> and others have contributed to the literature dealing with this subject. Zanda,<sup>13</sup> Cruveilhier,<sup>14</sup> and others have reported an occurrence of bone in the cerebral meninges; Pollack<sup>15</sup> and Poscharissky<sup>16</sup> in the lymph nodes; Morpurgo<sup>17</sup> in the bladder mucosa; Laboulin,<sup>18</sup> Huartado<sup>19</sup> and Pollack in the pleura; Ponfick,<sup>20</sup> Roepke<sup>21</sup> and many others in the muscle; Pollack in the calcified uterine myoma; Cornil and Ranvier<sup>22</sup> in the liver; Ribbert<sup>23</sup> in the suprarenal capsule; Klebs,<sup>24</sup> Knapp<sup>25</sup> and others in the eye; Adachi,<sup>26</sup> Outerbridge<sup>27</sup> and others in the ovary, and elsewhere.

Theoretical considerations of the heteroplastic bone formation have been given much prominence by various authors, notably von Hansemann, Ribbert, Bunting, Buerger and Oppenheimer and Pollack. The contentions of these authors may be summarized as follows:

1. Embryonic misplacement after the hypothesis of Cohnheim.
2. Metaplasia of connective tissue after the manner of callus formation.
3. Erosion of calcific deposit with the formation of vascularized spaces containing young connective tissue which assumes the role of osteoblasts.

Bunting disposes of the hypothesis of embryonic misplacement on the ground that the occurrence of the aberrant bone formation is too frequent to be explained on such a basis, that the bone formation occurs in connection with sclerosis and calcareous degeneration and that the experimental production of aberrant bone as carried out by Barth,<sup>28</sup> Sacerdotti<sup>29</sup> and Frattin has demonstrated that when a favorable condition exists which gives a proper stimulus to young connective-tissue cells the metaplasia of these cells into osteoblasts can occur. This proper stimulus is assigned by Bunting to calcium salts present in the lime deposits. The metaplasia theory is further supported by the fact that in practically all the cases

<sup>4</sup> Virchows Arch., 1900, vol. clxii.

<sup>5</sup> Cited by Poscharissky.

<sup>6</sup> Nothnagel's Handbuch, 1901, vol. xv.

<sup>7</sup> Virchows Arch., 1901, vol. clxvi.

<sup>8</sup> Virchows Arch., 1901, vol. clxvii.

<sup>9</sup> Ergebn. d. allg. Path. u. pathol. Anat., 1904, vol. ix.

<sup>10</sup> Jour. Exp. Med., 1906, vol. viii.

<sup>11</sup> Jour. Med. Research, 1907, vol. xviii.

<sup>12</sup> Jour. Exp. Med., 1908, vol. x.

<sup>13</sup> Ziegler's Beitr., 1889, vol. v.

<sup>14</sup> Traite d'anat. pathol. general, 1894.

<sup>15</sup> Virchows Arch., 1901, vol. clxv.

<sup>16</sup> Ziegler's Beitr., 1905, vol. xxxviii.

<sup>17</sup> Cited by Poscharissky.

<sup>18</sup> Idem.

<sup>19</sup> Idem.

<sup>20</sup> Cited by Buerger and Oppenheimer.

<sup>21</sup> Langenbeck's Arch., 1907, vol. lxxxii.

<sup>22</sup> Manuel d'histologie pathol., 1901, vol. i.

<sup>23</sup> Geschwülstlehre, 1904.

<sup>24</sup> Pathological Anatomy, vol. i.

<sup>25</sup> Arch. f. Aug. u. Ohrenheilk., 1871, vol. ii.

<sup>26</sup> Zentralbl. f. allg. Pathol. u. path. Anat., 1913, vol. xxiv.

<sup>27</sup> AM. JOUR. MED. SC., 1916, vol. cli.

<sup>28</sup> Ziegler's Beitr., 1895, vol. xvii.

<sup>29</sup> Virchows Arch., 1902, vol. clxviii.

reported in the literature the bone has been formed in young proliferating connective tissue in the neighborhood of calcific deposits.

As regards the cause of invasion by the young connective tissue and bloodvessels, Paul has suggested a trauma such as a fracture of calcific plates. Bunting upholds this suggestion and cites Howse's case of ruptured axillary artery, and Cohn's case of traumatized crural artery, and presents his own case in which signs of hemorrhage and old inflammatory exudates were found as supporting evidences in favor of this view.

The metaplasia theory encounters a few opponents, among whom Ribbert and von Hanseemann<sup>30</sup> may be mentioned. Ribbert, in his monograph on tumors, states that metaplasia of connective tissue into bone occurs only when there have been cells belonging to the osseous system, and therefore such a change is not a metaplasia in the strict sense of the word. Von Hanseemann believes that the aberrant bone originates in the misplaced islands of cartilage or perichondrium.

Whether or not the bone found in the thyroid, breasts, eye and elsewhere in the structures which are contiguous with cartilage originates in accordance with Hanseemann's view cannot be definitely decided, but such a mode of bone formation so frequently to be encountered in the lung, in the liver, and in the arterial walls cannot readily be conceived. Such is the stand taken by the supporters of the metaplasia theory as regards the contentions of Ribbert and von Hanseemann.

Two views are supported by Bunting as regards the mode of metaplasia involved in aberrant bone production, namely: (1) there may be a direct metaplasia of connective tissue into osteoid (callus) tissue with subsequent conversion into bone, and (2) resorption of calcific material by bloodvessels and young connective-tissue cells, formation of bone marrows and deposition of bone in the periphery by an osteoblastic membrane derived from the metaplasia of the connective-tissue cells accompanying the vessels.

In Bunting's case a cellular marrow was found. This contained mononuclear cells of myelocyte type, many of which with eosinophilic granules, polynuclear cells, both eosinophilic and neutrophilic, lymphoid cells and cells of erythrocyte series, non-nucleated cells and normoblasts. Thus the marrow space described by this author corresponds closely to the normal bone-marrow. These elements of bone-marrow are attributed by Bunting either to a metaplasia of the connective-tissue cells or to a metaplasia of the emigrated cells from the blood stream which are capable of further differentiating into various types of cells.

In 1907 Harvey experimentally produced bone in the rabbit's aorta by an application of irritants to its wall. Here again the cal-

<sup>30</sup> Berl. klin. Wehnschr., 1900, vol. xxxvii.

cific deposits were found to be closely associated with the production of bone.

Buerger and Oppenheimer, in 1908, reported a case of multiple bone formation in the sclerotic arteries and discussed at length the various features of heteroplastic bone formation. They follow Cohn, Pollack, Moenckeberg and Bunting in upholding the theory of metaplasia, but differ from Paul and Bunting in maintaining that the proliferation and invasion of the young connective tissue are brought about not only by trauma, but may occur in connection with organizing thrombus, canalization and vascularization of obliterating intima and the disease of the media. They further pointed out that in their case, at any rate, the cartilage was never transformed into bone.

In his recent monograph on neoplasms Ewing<sup>31</sup> mentions a certain alteration in calcium metabolism as one of the causative factors in heteroplastic bone formation. In fact, Thayer and Haven<sup>32</sup> have recently reported a case in which an excessive intake of calcium resulted in a deposition of calcium salts at the site of a chronic inflammatory lesion of the breast.

In the present study the abundance of degenerating cartilage and an evidence of endochondrial ossification first suggested a possibility of a previous tubal pregnancy, with subsequent absorption of all the embryonic tissues except cartilage. The clinical history is negative as regards this possibility. Even if it be assumed that the patient's own account of her previous history was inaccurate and that the tubal pregnancy had, indeed, occurred, it is certain that this pregnancy could not have taken place later than at least three years ago. The myoma which has occupied the uterine canal and has caused an intermenstrual bleeding for the past three years would have prevented an impregnation from taking place later than the onset of the present illness. It is inconceivable that even a cartilage could have remained preserved for this length of time. Although circumstances may differ in some respects, an observation made by Barth that a piece of bone introduced into the peritoneal cavity of the rabbit has been partially absorbed within six weeks' time is of some significance in this connection. Furthermore, the distribution of cartilage and bone found in this case involves practically the entire circumference of the tube. Such a distribution also is an argument against the hypothesis of the fetal remains. Finally, the presence of the osteoid tissue in conjunction with bone suggests that there has been a bone-formation independent of the cartilage.

Von Hanseman's theory on the origin of the heteroplastic bone appears here untenable. To assume that during the embryonal life a perichondrium or cartilage has been misplaced in such a

<sup>31</sup> Neoplastic Diseases, 1919.

<sup>32</sup> Jour. Exp. Med., 1907, vol. ix.

manner as to make it lie dormant in the Fallopian tube is merely hypothetical. Furthermore, it seems impossible that either perichondrium or cartilage, or any single tissue for that matter, can alone be involved in the process of embryonic misplacement.

The facts observed in this case, that in the capillary area of the mesosalpinx there are still left several foci of calcific deposits in the small bloodvessels which have undergone a hyaline thrombosis, and that in this area there are evidences of hemorrhage and chronic inflammatory reaction, and in addition that there are bone spicules formed in the osteoid tissue suggest that a transformation of the connective tissue into osteogenetic tissue has occurred. It is further probable that most of the calcific deposits have been resorbed in the process of metaplasia some time previous to the date of the operation.

At this point it seems advisable to define the use of the term "metaplasia," since there is a considerable confusion among the authorities. The term as it is applied in this communication is an extension of the definition given by Orth, namely, a transformation of one differentiated tissue into another differentiated tissue *either directly or indirectly through the medium of a less differentiated form of the original tissue*.

The presence of cartilaginous tissue, which in no place is entirely healthy but shows either more or less retrograde changes or ossification, and its close association to many of the young bones found in this case, seems to point to a primary metaplasia of connective tissue into cartilage, with a subsequent conversion into bone. Thus there seem to be two distinct processes involved in the formation of bone. On the one hand, there may have been a resorption of calcific deposits by the proliferating connective-tissue cells and bloodvessels which have invaded the calcified area in the course of inflammatory reaction, the conversion of the connective-tissue cells into bone-forming cells and the deposition of osteoid tissue by these cells. On the other hand, there may have been a metaplasia of the connective-tissue cells into chondrogenetic cells and a subsequent endochondral ossification.

By what mechanism a connective tissue may be transformed into cartilage cannot be made out in the present case, since there has been no new forming cartilage to be found. It is also uncertain as to how the process of the ossification of cartilage may have been initiated. Whether the disintegrating cartilage cells might become osteogenetic or not is impossible to say. Geddes<sup>33</sup> has stated that in many respects cartilage cells cannot be differentiated from osteoblasts. This point plainly needs a further experimental investigation.

<sup>33</sup> Jour. Anat. and Physiol., 1912, vol. xlvii.

**Summary and Conclusion.** 1. A case of aberrant bone formation in the Fallopian tube is presented.

2. Both cartilages undergoing ossification and calcific deposits, with surrounding organization tissue, some of which has been converted into an osteoid tissue are present.

3. Metaplasia of connective tissue into bone, both with the formation of cartilage and with the production of osteoid tissue is assumed to have occurred.

4. The possible mechanism involved in the conversion of the connective tissue into cartilage and of the cartilage into bone is left for a future experimental investigation.

## MERCURY BICHLORIDE INTRAVENOUSLY.<sup>1</sup>

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THE intravenous administration of mercury bichloride is a comparatively recent method of treatment. Osler gives it passing mention in the eighth edition of *Principles and Practice of Medicine* (1914) under the treatment of Syphilis. Baccelli, of Rome, began using it in 1917 in the treatment of gonorrheal arthritis, claiming excellent results. Within more recent years mercury salts have been advocated for intravenous injection in syphilis by R. L. Spittel, of England,<sup>2</sup> and E. F. Sanz, of Spain;<sup>3</sup> in the treatment of enlarged spleen due to chronic malaria by Greig and Ritchie of Calcutta, India;<sup>4</sup> in influenza by G. Ferrarini, of Italy;<sup>5</sup> in puerperal septicemia by J. A. Perez,<sup>6</sup> of Spain, in gonorrheal arthritis, erysipelas, influenza, anthrax and pyelitis, by Victor G. Vecki, of San Francisco.<sup>7</sup>

The technic of injecting mercury bichloride intravenously is very simple. The mercury bichloride is dissolved in normal salt solution, 10 c.c. of the solution containing 1 grain of the drug. The bichloride solution may be kept in a glass-stoppered bottle or it may be distributed in ampoules in amounts of 1, 2, 3, 4 and 5 c.c. each. Treatment is begun with 1 c.c. of the solution, which contains gr.  $\frac{1}{10}$  mercury bichloride. A tourniquet is applied above the elbow, the skin over a prominent vein is cleansed, the needle, preferably a fine, long, platinum needle is carefully introduced, so that the point rests free in the lumen; the tourniquet is now removed and the solution

<sup>1</sup> Read before the Lancaster County Medical Society, October 18, 1919.

<sup>2</sup> Practitioner, London, October, 1918, p. 212.

<sup>3</sup> Medicina Ibera, Madrid, August 17, 1918, p. 187.

<sup>4</sup> Indian Jour. Med. Res., Calcutta.

<sup>5</sup> Riforma Medica, Naples, November 9, 1918, p. 893.

<sup>6</sup> Medicina Ibera, Madrid, August 3, 1918, p. 130.

<sup>7</sup> Jour. Am. Med. Assn., May 31, 1919, p. 1596.

injected slowly. The needle is then withdrawn and the solution hastened through the vein by the patient raising his arm over his head and alternately closing and opening his fist.

Advantages claimed for this method over the other modes of mercury administration are that quicker results in treatment are obtained, a more accurate grading of dosage is made possible, and the course of the disease can be more closely observed, since the patient is seen oftener than is the case with other methods of treatment, and in the case of syphilis, frequent opportunity is given to obtain blood for the Wassermann reaction.

The intravenous injection of mercury bichloride is a comparatively safe procedure, and altogether painless and free from alarming reactions, immediate or late, provided certain very simple precautions are observed. One of these is that the needle should enter the vein and its point lie free in the lumen of the vein before injection is begun. This is to avoid injecting the drug outside the vein or into its wall and thus guard against the chief objection to this method, namely, pain at the site of injection and occlusion of the vein by a thrombus. Another precaution is that of using dilute solution of mercury bichloride. Concentrated solutions often cause a spasmodic contraction of the wall of the injected vein and a permanent occlusion of its lumen. Dr. H. S. Newcomer, of Philadelphia,<sup>8</sup> describes this condition in connection with arsphenamin injection: "There is a local reaction of the veins used for injection, which is fairly common. . . . Sometimes when one is injecting salvarsan into a vein which lies for a considerable distance superficially in the skin, the vein will be seen to contract throughout its entire length and become like a whipcord. The salvarsan ceases to flow and the condition continues for some time. Under some circumstances this contraction remains and is followed by thrombosis. The thrombosis may occur without the contraction having been superficially noticed. . . . Localized thrombosis certainly sometimes occurs, due to injury to the vein, because of faulty technic; but the reaction undoubtedly occurs when the injury to the veins is out of question, when the vein is large and free and the needle small and sharp. It occurs more frequently as the NaOH in the salvarsan is increased. It is more common in colored people than in white people." Another precaution to be observed is that of using a small needle; a one-inch gauge 25 platinum needle serves the purpose well. A large needle causes more pain, enters the vein with more difficulty and causes more injury to the vein. One more precaution. Treatment should be begun with a small dose, not over gr.  $\frac{1}{16}$  of the drug, and increase should be gradual and cautious. The injections can be given as often as once a day, but an injection every other day or three times a week is safer. This is continued

<sup>8</sup> AM. JOUR. MED. SC., August, 1919, p. 159.

until signs of mercurialism appear, when the injections are reduced to one or two a week.

The routine I have been following for some time in cases of syphilis is to give the mercury bichloride injections three times a week, starting with gr.  $\frac{1}{10}$ , giving gr.  $\frac{3}{20}$  to gr.  $\frac{2}{10}$  the second dose, gr.  $\frac{2}{10}$  to gr.  $\frac{1}{4}$  ( $\frac{5}{20}$ ) the third, and gr.  $\frac{3}{10}$  the fourth. In the case of a strong man the dose can be thus gradually increased to gr.  $\frac{1}{2}$ . As soon as signs of saturation appear, usually a slight soreness in the teeth if the jaws are shut with a snap, it is considered that the maximum dose for that patient has been reached and treatments are then given once or twice a week. Treatments are persisted in for at least six weeks; longer if the Wassermann reaction remains positive. I have often noticed when a patient has developed salivation that his tolerance for the drug after symptoms of salivation have disappeared has increased, and treatment can be resumed where left off without fear of salivation.

If mercury bichloride in normal salt solution is added to blood serum, an albuminate is precipitated which quickly dissolves on shaking and remains in solution indefinitely if the mixture is heated for thirty minutes at  $56^{\circ}$  C. If an excess of mercury bichloride is added the albuminate precipitates and does not redissolve, except by the addition of more serum or normal salt solution. Precipitation of mercury albuminate takes place if the mercury bichloride in the mixture is in excess of 1 to 300 or gr. 1 in 18 c.c. It may be assumed that these test-tube changes take place when the mercury bichloride solution is injected into the vein, for if some blood is allowed to mix with the bichloride solution in the syringe it will be noticed that the blood is not coagulated, but that a white cloud appears as the serum mixes with the bichloride solution, while the red cells sink to a lower level and remain unchanged. The leukocytes, however, will be found to have been destroyed by the bichloride. This statement is based on microscopic examination.

That mercury bichloride is exceedingly toxic and corrosive is well known, and it could not be used intravenously if it were not instantly converted into a non-corrosive albuminate. That the albuminate is comparatively harmless may be deduced from the fact that it is found in the circulating blood for several days after a single injection. In a case of bichloride poisoning fatal on the tenth day after ingestion, Rosenbloom,<sup>9</sup> of Pittsburgh, found that almost one-third of the mercury recoverable from the body was obtained from the blood alone.

Investigations into the pathology of mercury-poisoning are numerous and exhaustive, but nowhere can one find even an allusion to the pathology, if there is any, that follows therapeutic doses of mercury. The kidney seems to suffer most commonly in mercury-

<sup>9</sup> AM. JOUR. MED. SC., March, 1918, p. 348.

poisoning. I have not so far observed any kidney lesion that could be attributed to the effects of mercury bichloride. In fact, several cases that presented, besides syphilis, mild degrees of nephritis, pyelitis and cystitis, promptly cleared up under intravenous mercury bichloride injections.

The one serious drawback to the intravenous injection of mercury is the frequent occurrence of thrombosis in the injected veins. The condition is not very painful but possesses the potential danger of causing embolism, and may preclude the continuation of the method itself by occluding all the available veins as well as bring the skill of the operator in question. The accident is somewhat less frequent if the mercury bichloride is suspended in serum before injection,<sup>10</sup> but this modification is by no means thrombosis proof. Realizing this to be a serious drawback to the method I must hesitate to advocate its adoption by the profession as a routine practice. But in cases where quick results count for more than the local discomfort and slight chance of embolism would compel us to be cautious this method finds a proper place of application. Some day we may be in possession of a mercurial that is free from these objectionable features and equally as good or better than mercury bichloride in curative value. In that case the intravenous use of mercury will become as universal as that of arsphenamin is today. This is not an inspired prophecy, for experiments have been under way since 1915, conducted by Dr. Schamberg<sup>11</sup> and his coworkers to produce such a mercurial.

<sup>10</sup> The Treatment of Syphilis with Mercurialized Human Serum, Nebraska State Med. Jour., August 19, p. 230. By the Author.

<sup>11</sup> Jour. Am. Med. Assn., May 19, 1917, p. 1458.



## REVIEWS

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THE NOSE, PARANASAL SINUSES, NASOLACRIMAL PASSAGEWAYS AND OLFACTORY ORGAN IN MAN. By J. PARSONS SCHAEFFER, A.M., M.D., Ph.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy of the Jefferson Medical College of Philadelphia. Pp. 370; 203 illustrations. Philadelphia: P. Blakiston's Son & Co., 1920.

DR. SCHAEFFER describes his book as a "genetic, developmental, and anatomico-physiological consideration," and the work is the outgrowth of extensive studies along these lines conducted at the Yale, Cornell and Jefferson Medical Schools. It is the record of a great amount of work done and should be of much value to the student of anatomy of the special regions indicated in the title. It is, however, purely a scientific treatise on anatomy without any application to surgery, and as such will probably fail to excite the interest of specialists devoted to the practical rather than the theoretical side of medicine. Not that it should be so, for a knowledge of embryology and anatomy should be the invariable basis for all future work in any of the specialties, especially the surgical specialties, although unfortunately this is often overlooked. Neither will the work appeal to the undergraduate student of medicine for the simple reason that his hours, if not his brain, are already too overburdened to make a study such as this seem to him of importance.

As a scientific, painstaking effort this anatomy deserves a great deal of commendation, both on account of the work involved in its preparation, the subject-matter and its admirable arrangement, the great amount of information it contains and the splendid illustrations, most of them original, with which the text is largely interspersed. Many of these are of a distinctly original type, showing sections and dissections of the human fetus and skull made in a unique manner and different from the ordinary text-book presentation of the subject.

General and embryology and development of the skull and special organs comprises the opening chapter, and there is a discussion of congenital defects and so-called anomalies, though Dr. Schaeffer deprecates the use of this term, contending that as there is no fixed type, all organs show some deviation that might be called anomalous. For descriptive purposes, however, the average of the type must be used.

Following this initial chapter the "definitive nose" is thoroughly discussed, and in a most interesting manner. This includes the general nasal architecture, the lateral nasal wall and the septum. Then the various sinuses are taken up in detail, a chapter to each, beginning with the embryology and following the development through childhood to adult life.

But the unusual chapters are those devoted to the nasolacrimal passages—the nasal mucous membrane, the nerve, blood and lymph supply of the nose, and the olfactory apparatus proper.

While much of the subject-matter in these chapters is embryology, and, as such, will be passed over by the average casual student as too deep, or dry, or difficult, the reviewer contends that such should not be the case, and heartily recommends Dr. Schaeffer's book to all students of the head who desire true knowledge of this subject.

G. M. C.

PUBLICATIONS OF CORNELL UNIVERSITY MEDICAL COLLEGE.  
STUDIES FROM THE DEPARTMENTS OF PATHOLOGY, BACTERIOLOGY  
AND HYGIENE. New York, 1916-1918, Vol. XVI.

THIS volume embraces a collection of reprints of twenty papers published in various medical journals, five being devoted to researches in bacteriology, five to immunology and ten to histopathology; all are of much interest and value, and are indicative of the research activity of the above-mentioned departments.

J. A. K.

TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION. Vol.  
XXXVII, illustrated. Philadelphia: Wm. J. Dornan, 1919.

THIS volume contains 34 articles, all dealing with questions in surgery that are occupying the thoughts and efforts of the profession of today. The greater proportion of the contributions is based on the experiences and the knowledge gained from the same in the recent war. As a result of these advantages of experience, many of the obscure and baffling conditions have had developed a greatly improved method of treatment.

Two or more articles on wounds of the knee-joint outline most clearly the most recent advances in treatment, putting it now on a rational, well-understood basis.

The same can be said of wounds of the chest, chronic empyema and thoracic fistula treatment.

Exemplary articles also present surgical problems of reconstruction of peripheral nerve injury, bone transplants, cranioplasty,

fracture of the femur, splenectomy in anemias and many others worthy of mention.

The reviewer has derived much pleasure and instruction from the reading and studying of these transactions.

E. L. E.

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THE PRINCIPLES OF GYNECOLOGY, A MANUAL FOR STUDENTS AND PRACTITIONERS. By W. BLAIR BELL, B.S., M.D., Gynecological Surgeon, Royal Infirmary, Liverpool. Third edition. Pp. 660; 392 illustrations. New York: William Wood & Co., 1920.

THE appearance of a third edition of this book in less than three years after the second edition is evidence in itself that the work has been well received and is in demand. The present edition has been extensively revised throughout, although the bulk of the book is not greatly increased. Some new illustrations have been added and an improved quality of paper makes the book more attractive. The colored plates presented, although few in number, are unusually good, the coloring being as true to the actual natural color as can be produced. The author retains his arrangement of the subject-matter under pathological headings, and states that, despite objections, it is the only logical way to arrange a book of this kind. It is to be regretted that radium is given such scant attention in the treatment of myopathic bleeding and is not even mentioned in connection with cancer of the uterus. The chapter on electrotherapy has been deleted, but occasional mention of electrical treatments is made in connection with the treatment of various disorders. The misspelling of the word "Fallopian" occurs so generally throughout the book that mention must be made of it. On the whole, the present edition is distinctly more attractive than its predecessors.

F. B. B.

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THE AMEBÆ LIVING IN MAN. By CLIFFORD DOBELL, M.A., Assistant Professor of Protistology and Cytology, Imperial College of Science and Technology, London. Pp. 155; 5 plates with 94 figures. New York: William Wood & Co.

THIS latest contributor to our knowledge of amebiasis is a British zoölogist, who during the war had the opportunity of examining thousands of cases of infestation in the British troops. After a brief discussion of methods of fixing and staining the author traces the development of knowledge of amebiasis from the first description in the middle of the last century, through the period of confusion that reigned in the differentiation of parasitic from non-

parasitic forms, to the more accurate information of the present day.

The bulk of the monograph is devoted to *E. histolytica* and *E. coli*, the organisms on which his own work was done. He recognizes the now generally accepted harmless role of the latter as well as the frequent occurrence of *E. histolytica* in patients who have no symptoms of infestation. The organisms are considered exhaustively from the biological viewpoint without going into questions of treatment.

When, however, he comes to the description of the amebæ of the mouth, urine and various organs the author's views run counter to those of many observers in this country. *E. gingivalis* and, in fact, all amebæ except *E. histolytica* are regarded as harmless symbions. The bibliography drawn up by the author is extensive, but, unfortunately, in the case of *E. gingivalis* and less-known amebæ, does not include some of the more important American papers to which he has not had access.

Another peculiarity is the restriction of the generic term *endameba* to the form described by Leidy as occurring in the cockroach, while a separate genus of *entameba* is made to include the common man-infesting organisms.

M. M. E.

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**SURGICAL SHOCK.** By GEO. W. CRILE, M.D., Professor of Surgery, Western Reserve University, and WILLIAM E. LOWER, M.D., Associate Professor of Genito-urinary Surgery, Western Reserve University. Second edition, thoroughly revised and rewritten. Pp. 272; 75 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

ENRICHED enormously by their experience in the civilian clinic and even more so in the field and base hospitals in France, the authors have rewritten and enlarged their work on anoci-association. As in their first work they present as concisely as possible the principles upon which the doctrine of "anociation," the latest term supplanting that of "anoci-association," is based. All shock theories and their discussion are omitted.

A very long chapter is devoted to the pathology of shock of all kinds, and much that has been taught in the past has been proved true or untrue, as the case may be.

In the chapter on treatment special emphasis is laid upon physiological rest: (morphin) rest liquids, transfusion, nitrous oxide gas anesthesia, local anesthesia or a quick operation.

Morphin is contra-indicated in cyanosis; stimulants are a harm in most instances. Soda solution is next best to blood for transfusion. Solutions other than blood are best given by mouth, bowel or skin in preference to intravenous.

Chapter V outlines in detail anociation technic in general. Later chapters take up each separately, the anociation treatment of specific operative cases, *i. e.*, abdominal operation, appendicitis, gastric surgery, gall-bladder, etc. Separate chapters are devoted to goitre, anociation and blood transfusion.

After many of the chapters is appended a list of "don'ts," which admirably sums up the ideas the authors are striving to drive home.

E. L. E.

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REPORT FROM THE PATHOLOGICAL DEPARTMENT AND THE DEPARTMENT OF CLINICAL PSYCHIATRY OF THE CENTRAL INDIANA HOSPITAL FOR THE INSANE, Indianapolis, Indiana, 1915-1917, Vol. VII, pp. 684.

THIS volume summarizes the course of instruction given in nervous and mental diseases and in neuropathology by the faculty of the Indiana University School of Medicine in this hospital, and gives a complete, interesting and valuable summary of the activities of the institution during 1915-1917; 209 pages are devoted to case histories in clinical psychiatry and 423 pages to pathological reports, mainly accounts of necropsy examinations. The volume also contains fifteen papers published by the staff during 1916-1917 and a good index; it reflects great credit upon the institution and its staff, and should prove of much value to those interested in clinical psychiatry, mental pathology and neuropathology.

J. A. K.

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HANDBOOK OF SKIN DISEASES. By FREDERICK GARDINER, M.D., B.Sc. (Public Health), F.R.C.S.E., Lecturer on Skin Diseases, University of Edinburgh; Physician for Skin Diseases, Royal Infirmary, Edinburgh. Pp. 160; 46 illustrations. Edinburgh: E. & S. Livingstone. New York: William Wood & Co.

THIS small volume is based chiefly upon the lectures delivered by the author. The views expressed were mostly taught in the Edinburgh School. The subject is treated under fifteen headings and the following classification is employed: Streptococcal and staphylococcal infections; diseases due to animal parasites; seborrhea and the seborrheids: psoriasis; infections of the hairy scalp; urticaria, erythema and allied conditions; bullous eruptions of the skin; dermatitis; diseases due to light, pruriginous eruptions and lichen planus; pityriasis group; tuberculosis and the tuberculides; pigmentary changes and hypertrophies; infective warts, keloids and adenoma sebaceum; neoplasms; syphilis and the syphilides.

The introduction includes the anatomical structure, physiological functions, clinical pathology and the remedial agents used in the treatment of skin diseases. A few selected prescriptions are mentioned in the appendix as of use for the treatment of the common skin affections. The preparations given are largely used in the skin department of the Royal Infirmary, Edinburgh. The volume is compact and readable; naturally in such a small space extreme condensation is necessary and but a cursory review of the subject can be given. If criticism were given the space devoted to some of the rarer diseases might be used with advantage in making additions to the common affections of the skin. F. C. K.

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MANUAL OF SURGERY (ROSE AND CARLESS). By ALBERT CARLESS, Emeritus Professor of Surgery to King's College, London. Tenth edition. Pp. 1495; 676 illustrations. New York: William Wood & Company, 1920.

WHEN a text-book of surgery reaches its tenth edition it needs little encouragement from or can be affected only slightly or not at all by the comment of a reviewer. Rose and Carless is becoming to surgery what Gray for many years has been to anatomy, the great English book for medical students. Many others have sought favor and have ceased to appear, but this one remains and renews its contents at suitable intervals. It maintains through the years its text-book form and shows little tendency to become a book of reference. There are no references to the literature, but the editors gave and now Carless alone gives us a condensation and estimate of the value of the best contributions in the literature. Indeed, there is a minimum of mention of the names of individual writers and a maximum of what the editor thinks is the best thought and practice in connection with the various surgical conditions. The war has intervened since the last or ninth edition appeared and the additions to this edition are concerned chiefly with contributions coming from war experience. These have to do largely with the treatment of infected wounds, with compound fractures and with making good the defects of war wounds. Many new illustrations are added. It may now fairly be called a one-man book, so that reduplication is effectively avoided. This permits also what has been accomplished in an eminently successful degree, the absorption of a vast amount of literary material and its expression in a terse, lucid and full discussion of each subject. We have here above everything else a student's text-book, one that lives up to the reputation of the best of its kind. There has been much discussion as to whether this kind of text-book can be of real value to the student. In the reviewer's opinion we have not yet out-

lived the necessity for it, since the best kind of a clinical and demonstrative course on surgery cannot cover the whole field. Let anyone who entertains the opposite view first estimate the number of cases appearing in the best clinical course of which he has knowledge, and then compare these with the subjects covered in a good text-book and see how many conditions have been missed in the clinical course. There will be many times more missed than have been covered. It would be difficult to find any important ordinary surgical condition which has not been discussed in this volume in a manner sufficiently satisfactory for an undergraduate medical student, or, for that matter, most practitioners. Not all surgeons will agree with every statement made and some would like to see reference to war work not taken up, as Duval's brilliant contribution on lung surgery; but when everything else has been said, it will remain a great text-book for students.

T. T. T.

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COMMON DISEASES OF THE SKIN. By G. GORDON CAMPBELL, B.Sc., M.D., C.M., Lecturer on Dermatology and Pediatrics, McGill University; Physician to the Montreal General Hospital. Pp. 229; 177 illustrations. New York: Macmillan Company, 1920.

THE writer has endeavored to provide illustrations and a short description of some of the commoner diseases of the skin, with a few lines on differential diagnosis and methods of treatment. The diseases which have been chosen for the present volume were selected from the statistics of the hospital clinic with which the writer was connected, thereby, possibly, admitting some not properly classed as common because of the large proportion of aliens in his clientèle. In a volume of this size the satisfactory method has been employed of describing the various diseases alphabetically. The dermatological conditions mentioned are as follows: Acne, alopecia, alopecia areata, carcinoma, chloasma, dermatitis medicamentosa, dermatitis repens, dermatitis venenata, eczema, eczema seborrheicum, erythema multiforme, erythema nodosum, favus, furunculus, herpes simplex, herpes zoster, ichthyosis, impetigo contagiosa, keloid, keratosis pilaris, lichen planus, lupus erythematosus, miliaria, miliaria crystallina, milium, nevus, pediculosis, pityriasis rosea, pruritus, psoriasis, purpura, ringworm, scabies, seborrhea, sycosis vulgaris, syphilis, tinea versicolor, tuberculosis, urticaria, verruca, vitiligo.

The author's purpose has been accomplished in providing many and excellent photographs, which serve to illustrate splendidly the diseases of the skin commonly met. The type is large and legible and the paper excellent.

F. C. K.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**An Electromyographic Study of Chorea.**—COBB (*Bull. John Hopkins Hosp.*, 1919, xxx, 35) finds that choreiform movements give an electromyogram similar to that of a short normal voluntary muscular contraction. Inability to maintain voluntary contraction is clearly shown in the electromyogram. Weakness of muscular contraction is shown electromyographically by lessened electrical discharge.

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**Electromyographic Studies of Clonus.**—COBB (*Bull. Johns Hopkins Hosp.*, 1918, xxix, 247). The studies were made with the string galvanometer for electrocardiographic work. The string used consisted of a gilded quartz fiber 3 micra in diameter with a resistance of 5000 ohms. The author finds that electromyography is a more accurate and more easily applied method for the study of muscular phenomena than those formerly applied to clinical observation. Clonus gives a characteristic electromyogram. Fatigue does not affect the rate of clonus. Increased stimulus increases the rate of clonus and the size of the electromyographic wave but does not change the rate of the active current. The number of active currents per contraction varies with the type of the clonus.

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**Pericarditis with Effusion and Experimental Studies.**—WILLIAMSON (*Arch. Int. Med.*, 1920, xxv, 206). In pericardial effusion the fluid accumulates first along the lower margin of the heart and about the



apex, particularly on the diaphragmatic surface of the heart. With small effusion this is the only place in which fluid accumulates with regularity. The result of the accumulation of the fluid in this position is to push down the left lobe of the liver. This was demonstrable in practically every case, and in many cases it was a very conspicuous feature. Special stress should be laid on this as an early diagnostic sign. The second place in which fluid accumulates is over the great vessel at the base. With small effusion it is occasionally present in sufficient amount to be detected by percussion. With medium-sized effusion this layer is generally thick enough to be demonstrable by percussion and this retrosternal dullness is an important diagnostic sign. With both small and medium-sized exudate we were neither able satisfactorily to demonstrate percussion dullness in the fifth right interspace (Rotth) nor could a rousing of the cardiohepatic (Epstein) angle be made out in a single case. The behavior of the fluid is practically independent of the position of the patient with effusion of the side represented by the injection. In at least 14 of the 33 cases the anterior surface of the heart, in spite of the exudate, remained in part uncovered by the fluid, so that a pericardial friction rub could readily exist. This persistence of the pericardial rub is to be anticipated in cases in which the heart is relatively large, though there is still doubtless space between the vertebral columns at the sternum. From the standpoint of most readily reaching small amounts of fluid the most appropriate sites for puncture are either just outside the apex or in the chondroxyphoid angle.

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**Stereoroentgenograms of the Injected Lung as an Aid to the Study of the Lung Architecture.**—MILLER (*Bull. Johns Hopkins Hosp.*, 1919, xxx, 34). By the use of differential injective masses in the pulmonary arteries and veins the relation of these structures are plainly outlined by stereoroentgenograms. Even though the pulmonary arteries when injected can be recognized, stereoroentgenograms have comparatively dense linear markings along the lateral wall of the bronchi. Under similar conditions the main venous trunk can be made out on the mesial side of the thin bronchus but in its ultimate distribution its branches are not associated with the bronchi. In reading roentgen-ray plates care should be exercised in not mistaking these linear markings for densities produced by pathological changes. Ring-like shadows, with sharp borders that appear along the bronchi, are often due to the plane that the bronchi bear to the observer. When these ring-like shadows are broad, with irregular hazy borders, they are cast by bronchial cartilages. This study suggests once more the importance of a knowledge of lung structure in interpreting densities cast on the roentgen-ray plate. For general directions for the preparation of the differential injection mass which is especially applicable to the study of the distribution of the bloodvessels, see article by MILLER (*Anatomical Record*, 1918, xv, 47). The basis of the injection mass consists of a suspension of cornstarch in 70 per cent. alcohol to which vermilion granules are added. When it is desired to obtain a uniform dense shadow ultramarine blue granules for the less dense and finely granular shadow is desired in the differential injection mass by the use of a greater or less quantity of 70 per cent.

alcohol the injection mass can be made to penetrate to any desired distance within the lungs. If the bronchi alone are to be injected a thick vermilion mass gives the best result, for if the mass is too thin it will penetrate the air sacs and a blurred shadow will result or else the whole lung will appear solid.

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**Analysis of the Spread of the Excitation Wave in the Human Ventricle.**—FAHR (*Arch. Int. Med.*, 1920, xxv, 146) believes the excitation process begins first in the subendocardial layers of the Purkinje system in the neighborhood of the papillary muscle usually a little earlier in the right ventricle and spreads first to the apical layers causing the Q wave. The excitation process is quickly conducted to the basal arborization of the Purkinje system, giving rise to the anacrotic limb of the R. While the excitation process is being propagated through the basal Purkinje system the process in the apical area of the Purkinje system is spreading to the ordinary muscle fibers of the apex. By the time the peak of the R is reached the negativity in the ordinary muscle fibers of the apex is of sufficient magnitude to neutralize the preponderance in the basal Purkinje arborization and cause the catacrotic limb of the R and the ST. The process meanwhile is passing from the basal Purkinje system into the ordinary muscle fibers of the base. Their negativity increases until the effect of the apical fibers is counteracted and the S wave is produced. The negative process begins to die out at the apex, first leaving a preponderance of negativity at the base. This gives rise to the P wave. The form of the electrocardiogram in hearts which have left-sided enlargement is due to the increased length of conducting path in the left ventricle. The right ventricle receives the negativity first. In right-sided enlargement the ventricle receives the negativity first because the path of conduction in the right ventricle is longer. The form of the electrocardiogram in these cases is due to a preponderance of negativity of the left side. The diagnosis of right and left bundle branch lesion as commonly made is probably wrong. In the left bundle branch lesion we should find a high R in lead I and a deep S in lead III. In right bundle branch lesions we get a deep S in lead I and high R in lead III.

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**Colloidal Gold Reaction and Its Clinical Interpretation.**—WARWICK and NIXON (*Arch. Int. Med.*, 1920, xxv, 119). The authors believe that the colloidal gold test is the most delicate of the routine spinal fluid reactions and that with careful technic and proper attention to neutrality the special gold chloride solutions are within the reach of every laboratory worker. They believe that it does not replace any other test but is of independent value. It is of special importance in the early diagnosis of neurosyphilis. The various curves are not specific but of great diagnostic value in connection with other clinical and laboratory findings. A colloidal gold curve may be obtained with or without other positive findings after provocative treatment. The curve does not parallel clinical signs nor give definite evidence of improvement under treatment. Patients with no involvement of the central nervous system or who are non-syphilitic give no colloidal gold curve. Clear-cut

clinical cases of tabes dorsalis may show all the spinal fluid reactions negative both before and after treatment. A curve in zone 3 with a negative cell count and negative or faintly positive globulin is strongly suggestive of a brain or cord tumor or myelitis. Curves in zones 1 and 2 may be found in non-syphilitic conditions such as multiple sclerosis and brain abscess. A cell count above five the authors regard as pathological, but the cell count is of no value in indicating duration or severity of the process or improvement. The colloidal gold reaction should be included in every spinal fluid analysis and neurological examinations as well as in all cases of general syphilis.

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**A Clinical Study of Yellow Fever.**—ELLIOTT (*Arch. Int. Med.*, 1920, xxv, 174), from a clinical and pathological study of about seventy cases of yellow fever observed in Guayaquil, Ecuador, during the summer of 1918, considers clinically yellow fever is similar to infectious jaundice. The differences existing between the two diseases appear to be chiefly those of degree. There is more marked jaundice and less hemorrhage in yellow fever than in infectious jaundice. Although the hemorrhage is a usual occurrence in all severe cases, yellow fever is not a true hemorrhagic disease. The hemorrhage apparently follows necrosis of parenchymatous tissues and endothelial cells. The jaundice of yellow fever appears to be a non-toxic, dissociated, hepatic (suppression) type. Death appears to be due to uremia. It is usually preceded by anuria. There is an intense degeneration of the epithelium of the convoluted tubules. The glomeruli and collecting tubes remain relatively free from degeneration. Convalescence in all patients who survive is prompt. The complete restitution of all organs to normal is remarkable. No evidences of impaired liver or kidney function remain, although intense parenchymatous changes must have occurred.

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**Fluoroscopy of the Cerebral Ventricles.**—DANDY (*Bull. Johns Hopkins Hosp.*, 1919, xxx, 29) has previously shown that if air is substituted for the cerebrospinal fluid in the ventricles of the brain an accurate outline of the lateral ventricles can be cast in a roentgenogram. In this communication the author shows that the lateral ventricle when filled with air can be clearly seen under the fluoroscope. Twenty-five cases have been studied by this method. The results in adults are just as good as in children. By fluoroscopy hydrocephalus can be accurately diagnosed at all stages of its development. Several unsuspected cases of hydrocephalus have been demonstrated by the fluoroscope. The diagnosis of a false ventricular hernia (ventriculocoele) was made with certainty because the air from the ventricle could be seen to pass directly into the swelling. Fluoroscopy of the ventricle has practically the same range of utility as ventriculography, and almost the same results have been obtained. Following the injection of air in the ventricle both fluoroscopy and ventriculography should be used.

## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

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**Tubing as a Cause of Reaction to Intravenous Injection, Especially of Arsphenamin.**—From a study of the "tubing reaction" following the administration of arsphenamin through new tubing, STOKES and BUSMAN (*Jour. Am. Med. Assn.*, 1920, lxxiv, 1013) conclude that "A certain widely distributed brand of so-called pure gum rubber tubing seems to contain, when new, a toxic agent responsible for a definite type of reaction following the intravenous administration of arsphenamin, and possibly also of alkaline solutions and transfusion mediums." The toxic substance gradually disappears from the tubing on use. It is not destroyed by the ordinary sterilization by boiling, is insoluble in water, appears in toxic amounts in arsphenamin, dilute NaOH solutions, etc., merely by passing them through a new tube en route from container to vein, and is not apparently associated with the mechanically removable debris from the inner surface of the tube. The toxic substance is apparently removable in the first instance by soaking the tubing for six hours in normal NaOH solution and rinsing. The reaction induced by this toxic agent consists of chills coming on from thirty to sixty minutes after injection, with nausea, vomiting, diarrhea, a sharp rise in temperature, headache, lumbar cramps, etc. The reaction was induced by the authors in typical form in dogs.

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**Treatment of Leukemia with Deep Roentgenotherapy.**—ROSENTHAL (*Berl. klin. Wchnschr.*, 1919, lvi, 1113, abstracted in the *Journal of American Medical Association*, April 17, 1920) reports striking results in the treatment of leukemia with deep roentgenotherapy. In addition to the reduction in the number of leukocytes and diminution in the size of the spleen, the chief value lies in the disappearance of the subjective symptoms in cases in which other therapeutic methods had failed. He gives in detail the history of a case that has been observed now for three years in which after several treatments distinct improvement occurred. For five or six months after each treatment the patient felt well and was able to work, then there was a recurrence of symptoms promptly relieved by a new treatment. He considers that the roentgen ray is the most reliable treatment in leukemia. Severe reactions, however, do occur. He recommends that the treatment be intermittent.

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**Administration of Arsphenamin by Retention Enema.**—MANDRACCHIA (*Med. Record*, 1920, xcvi, 144) advocates the administration of arsphenamin by the retention enema method. In the gynecological section of

the Metropolitan Hospital this method has been employed in 25 cases representing the various stages of syphilis. Twenty per cent. of these cases have been completely cured serologically and clinically; 36 per cent. have improved clinically and the Wassermann reactions changed from four plus to two plus. In 40 per cent. the Wassermann reaction was unaffected but the patients showed marked clinical improvement. When these arsphenamin enemas were first started there was some apprehension as to possible local injury to the alimentary tract. About 500 of these enemas have now been given with no apparent injury. Mandracchia believes that the drug undergoes some chemical change in the intestinal tract. He concludes that there are no contra-indications to this method of administration and that the slow absorption is an advantage in preventing the production of nitroid crises. For the technic of the enema method of administering arsphenamin, the reader must consult the original article.

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**Inhalation Treatment in Pulmonary Tuberculosis.**—ROBINSON (*Med. Record*, 1920, xcvi, 143) believes that creosote is the only drug which, when properly used, is of real value in the cure of pulmonary tuberculosis. He generally uses a mixture of equal parts of beechwood creosotes spirit of chloroform and alcohol. Ten to twenty drops of this are poured upon the moistened sponge of a perforated zinc inhaler. With practice the patient can wear this inhaler almost constantly with little or no discomfort, the drops on the sponge being renewed whenever the odor of creosote becomes less appreciable. If creosote is given by mouth it should be in small, repeated doses. Given undissolved in capsules it is often upsetting to the stomach. During any treatment with creosote it is necessary to examine the urine every day or two; if albumin appears the length of time or the frequency of use must be lessened.

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**Experience with the Schick Test and Toxin-antitoxin and a Plea for Their Use in the Extinction of Diphtheria.**—LILLY (*Boston Med. and Surg. Jour.*, 1920, clxxxii, 110) has drawn the following conclusions from his experiences with the Schick test and the toxin antitoxin immunization of children susceptible to diphtheria. He believes that in institutions, schools or communities where diphtheria has been prevalent for a considerable period of time the universal taking of cultures is practically useless. A non-virulent bacillus is often found to be persistent in the throats of so-called chronic diphtheria carriers. He believes that repeated passive immunization does not protect and that such immunization lasts less than three weeks. He found that toxin-antitoxin does give absolute and persistent immunity to diphtheria when more than one month has elapsed after its administration. Reactions are much less frequent and severe. On the other hand, toxin-antitoxin has no curative properties and does not immediately protect against diphtheria. He is also of the opinion that the Schick test is not rapid enough to be of immediate use in cases exposed to clinical diphtheria and should be used only to separate immunes from non-immunes. The active immunization of non-immunes should be used to protect susceptibles when there is no immediate necessity to protect life. He believes that in the general use of the active immunization of non-immunes we have a means of exterminating diphtheria.

**Mercuric Chloride Poisoning from Vaginal Injections: Two Fatal.**—BLAND (*Jour. Am. Med. Assn.*, 1920, lxxiv, 1227) gives details of three cases of mercuric chloride poisoning following the vaginal injection of strong solutions for the prevention of conception or the induction to abortion. Two patients died, the fatal outcome being due to complete suppression of urine. In each case there was a violent local reaction for which local agents had been applied without relief. Details of the history and course of illness of each case are given, with blood analyses, etc. The treatment is not detailed. In the same issue of the *Journal* (p. 1230), De Porte gives the case of a woman who died from acute traumatic nephritis about twenty-four hours after the insertion of two 7.3 grain mercuric chloride tablets into the vagina to prevent conception.

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**A Comparison of Methods for Determining Thyrotoxicosis.**—From observations on a selected group of 11 cases, WOODBURY (*Jour. Am. Med. Assn.*, 1920, lxxiv, 997) concludes that complete methods of examination with special attention to the possibility of errors in case of psychoneurotic patients should furnish the basis for diagnosis, rather than reliance on any functional test, though these tests are of great value in the compilation of evidence, especially in relation to the degree of toxicity. He found the epinephrin chloride test clear, positive, and of moderate degree in 6 cases; clear, positive, and of more marked degree in 5. Basal metabolism results in the 11 cases were: 11 per cent. high; 6 per cent. low; 5 per cent. high; 8 per cent. high; 8 per cent. high; 20 per cent. low; 4.5 per cent. low; 14 per cent. low; 2 per cent. high; 7 per cent. high; and one, flat normal. Readings not varying more than 15 per cent. from the normal were regarded as normal. On section, the eleven thyroids all showed definite abnormalities of a type suggesting functional overactivity.

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**Meningitis Treated by Intrathecal Injections of the Patient's Blood Serum.**—The clinical features and the character of the cerebrospinal fluid in the case reported by WATERHOUSE (*British Med. Jour.*, January 10, 1920, p. 45) were typical of cerebrospinal fever, although the meningococcus was absent from the spinal fluid. The fact that the examination was not made until the eighth day of the disease probably accounts for their absence. On admission the patient appeared desperately ill and the next two days the symptoms increased in severity. It was therefore decided to try the effect of intrathecal injections of the patient's own blood serum. Five injections were given in all. Improvement set in from the time of the first injection and recovery was rapid and complete. Helmitol (at first 10 grains every four hours until hematuria appeared, when the dose was reduced by half) was also given, but the author attributes the recovery of an apparently hopeless case to the intrathecal injections of serum.

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**Studies on Experimental Pneumonia. IV. Results of Prophylactic Vaccination Against Pneumococcus Pneumonia in Monkeys.**—CECIL and BLAKE (*Jour. Exp. Med.*, 1920, xxxi, 519) found that subcutaneous inoculation of monkeys with pneumococcus Type I vaccine in doses

comparable with those employed in man did not protect them against pneumonia from either Type I or Type IV pneumococcus. However, invasion of the blood stream by pneumococcus in vaccinated animals was usually slight and the proportion of recoveries considerably higher. Pneumococcus saline vaccine, while failing to protect the animal against pneumonia, produced a greater amount of protective substance in the serum than did pneumococcus lipovaccine, and is probably a better antigen. The vaccination gave definite protection against experimental pneumococcus septicemia; thus, vaccination may induce a humoral immunity without protecting against intratracheal infection. A strict analogy cannot be drawn between pneumococcus immunity in monkeys and in man, since in the latter a considerable amount of resistance already exists, while monkeys are highly susceptible to pneumococcus infection.

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**Protective Inoculation Against Influenza.**—WYNN (*British Med. Jour.*, February 21, 1920, p. 254) advocates the use of a vaccine containing equal numbers of Pfeiffer's bacilli and various strains of pneumococcus and streptococcus recently isolated. With pneumococcus only first cultures are used, with streptococci either primary or first subcultures. He gives two doses, 200 million and after one week 400 million. During the epidemic period of 1918-19, of 680 persons injected only 14 developed influenza, and 4 of these were attacked three months after the last injection. In all cases the disease was mild and there was no pneumonia. Wynn reviews at some length results obtained from protective inoculation by both British and American observers.

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**The Therapeutic Value of Oxygen in Pulmonary Lesions: Preliminary Note.**—Observations on two cases of pneumonia, one of bronchitis, and on a normal individual, led MEAKINS (*British Med. Jour.*, March 5, 1920, p. 324) to conclude that in certain respiratory diseases when there is anoxemia of the arterial blood the administration of oxygen will diminish this anoxemia and so relieve the cyanosis. If the oxygen be given in sufficient concentration in the inspired air the arterial saturation with oxygen may be raised above normal in both normal individuals and those suffering from respiratory diseases. The method of administration was that devised by Haldane.

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**Severe Mercurial Stomatitis Caused by the Administration of Calomel.**—GORDIN (*Jour. Am. Med. Assn.*, 1920, lxxiv, 1163) reports two severe cases of mercurial stomatitis following the use of calomel as a cathartic: an acute case, in which the patient died on the seventeenth day after the ingestion of 2 grains of calomel and a case of thirteen years' standing showing the results after recovery. In addition to these 2 severe cases a number of milder cases of salivation have been seen by the writer. It is definitely known that the action of calomel as a cathartic is simply a mechanical irritation, due to the metallic mercury liberated, and that it has no action on the liver. He concludes that there are many efficient cathartics which are less dangerous than calomel.

## PEDIATRICS

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UNDER THE CHARGE OF

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**The Influence of Food upon Development.**—VAN DER BOGERT (*Arch. Ped.*, December, 1919) asserts that to suggest that diet is the sole or all-important factor in the prevention of disease is to court criticism as a faddist, but he speaks from an experience of twenty years, ten of which have been devoted to the treatment of children, which has convinced him that rational feeding in infancy and childhood has a real bearing upon the development of mental and physical strength in the adult and in the resistance to infection. Experience seems to show that the present-day civilized woman cannot produce a satisfactory milk for longer than one year. Babies kept longer at the breast usually develop less well, and do better when other foods, properly prepared and administered, are given. Physical defects and digestive disorders are frequent in the later life of children who give a history of having been long nursed at the breast. The real danger of prolonged nursing lies in the likelihood of overfeeding, since it practically always means breast milk in addition to other foods and much of the nursing is practiced at nights when the digestive organs should be at rest. The young carnivora remain with the mother for a period of a few weeks to even more than a year. Before they are weaned they begin to scrape off the meat from the prey that the mother brings home, and so gradually acquire a taste for their future food and an ability to digest it. This argues for gradual weaning, a gradual accustoming of the digestive organs to their future task, the early administering of green vegetable juices, fruit juice and beef juice. Prolonged bottle feeding frequently hinders development. The question of milk as a food in later childhood is of importance to be considered. Owing to certain propaganda as to the value of milk as a food, too much of it is being given to older children to the exclusion of other foods, or in addition to other foods. He advises small quantities of milk but a mixed diet of preferably three meals a day. Older children to develop normally must have digestive rest. At eighteen months he recommends three meals. There should be sufficient interval to insure digestion and a period of rest. He recommends a somewhat similar procedure in infants also; in the early months feeding every three hours, every four hours after six months and with longer periods at night.

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**Anatomical Considerations in the Rectal Prolapse of Infants.**—TODD (*Ann. Surg.*, February, 1920) places rectal prolapse in three types as follows: At the anal margin; at a certain distance above the anal margin and protruding; at a higher level (pelvic colon) and not protruding. The second and third of these types clearly belong to the class of intussusception, differing from the ordinary clinical condition only in that the entering portion of bowel commences its progress through



the intussusception low down in the distal colon or in the rectum. There are two locations favorable for the development of an intussusception, namely, the pelvirectal junction, and the subdivision of the rectum at the great valve of Houston. At both of these areas there is a more or less marked infolding of the bowel wall, and both correspond to the junction of a higher and comparatively mobile portion to a lower and more fixed portion. As regards the causes of rectal prolapse, especially of that type beginning at the anal margin, given in the literature, mention must be made of overloaded rectum, straining at stool, lack of muscular tone in the pelvic diaphragm, and diminution of fat in the ischioirectal fossæ in rickets and wasting diseases. Another factor is the fact that in infants the rectum is more vertically placed in the pelvis than in the adult, because of the more vertical position of the sacrum. From a study of anatomical material he finds that, estimated by the position of the great valve of Houston, the rectum at birth presents practically the same relation to the vertebral column as in the adult; that the rectal stalks are of the same proportionate lengths and therefore there is no greater laxity; that the only anatomical character which can be of importance in infantile prolapse are the comparative straight sacrum and the consequent more vertical rectum.

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**Is Fat Starvation a Causal Factor in the Production of Rickets?**—HUTCHISON (*Glasgow Med. Jour.*, January, 1920) says that there are two main lines of thought regarding the primary etiological factors in the causation of rickets. One follows the assumption that it is a disease akin to beriberi and scurvy, and is due to a deficiency in the diet of the fat soluble growth-producing factor. The other thought is that it is not a deficiency disease, but that it is caused by lack of exercise and want of fresh air during the period of development. Paton and Findlay believe that while the amounts of fat in the diets of non-rachitic families is on an average 10.7 per cent. higher than that of the rachitic, the overlap is so great that a defective supply of fat cannot be considered as playing an essential part in the causing of rickets. The author made a series of studies to determine that although the supply of fat is adequate the rachitic may not be able to absorb what is ingested, and that fat starvation is really present. He made three tests as follows: (1) To determine if there is an excessive loss of fat through pancreatic insufficiency; (2) to determine if there is an excessive loss of fat through the passage of unduly large movements; (3) to determine if there is any true defective absorption of fat. The first test showed there was no evidence of defective digestion of fat and therefore no defective absorption of fat from this cause. The second test showed there was no excessive loss of fat due to large stools. The third test showed there was no falling off in the absorption of fat, but it was shown that the more fat that was given the more the rachitic child would absorb. He was unable to show that calcium deficiency was brought about by defective fat assimilation.

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**Acute Cholecystitis in Children as a Complication of Typhoid Fever.**—REID and MONTGOMERY (*Bull. Johns Hopkins Hospital*, January, 1920) have collected 18 cases of typhoid fever in children under the age of fifteen who either died or were operated on for complications arising

in the gall-bladder. In 1 case the acute cholecystitis did not develop until eight months after recovery from this disease. In all the other cases the complication came on during the course of the disease. Eight patients died without surgical treatment. All of these cases occurred prior to 1893. Since that time 10 cases have been treated surgically. One of these died, making a mortality of 10 per cent. The records of the earliest were not supported by any bacteriological studies. In recent years cultures of the gall-bladder have usually been made at the time of operation. In this connection the leukocyte count is of interest. When cultures have shown a pure culture of typhoid bacilli, the count has usually been relatively low, usually about 10,000. In one case in which cultures were not made there was a leukocyte count of 33,000, and in another which showed an organism not definitely identified, there was a count of 21,000. Thomas in 1901 collected from the literature 154 cases of typhoid fever complicated by cholecystitis. Perforation of the gall-bladder occurred in 39 of these. Twenty-eight were not operated; 11 were treated surgically with a mortality of 54.6 per cent. In 1908 Ashhurst collected 21 cases of acute cholecystitis in which an operation was performed during the course of typhoid fever. Eight recovered. Price in 1916 collected 8 other operative cases, and added 1 of his own, bringing the total of cases to 30 cases. In the 9 collected cases of Price, there was 1 death and this was due to intestinal perforation, two weeks after the operation on the gall-bladder. The 6 cases reported in this paper all recovered.

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**Some Facts and Fallacies of Maternal Feeding of Infants.**—LOVE (*Southern Med. Jour.*) says that the gross appearance of breast-milk furnishes an unreliable index as to its suitability for the baby. Before pronouncing milk as being too rich in quality, the presence or absence of colostrum bodies should be determined by microscopical examination. The mere fact that milk is scant in quantity also furnishes no valid excuse for the withdrawing of the infant from the breast, but rather calls for supplemental feedings. Conclusions drawn from examinations of milk chemically are liable to be misleading. The laboratory findings should confirm clinical observation. In influencing the quality of breast milk the maternal dietary, while of some importance, is a smaller factor than causes which operate through the medium of the mother's nervous system.

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**Infant and Child Mortality.**—SCHWARZ (*Am. Jour. Dis. Children*, April, 1920) presents important statistics in this paper. The material was taken from the social histories of 10,000 families covering a period of ten years. These families were of heterogeneous nationalities, and their social status was that of the so-called working element. Because of the great amount of work involved and because of the economic situation of the world rendered this an opportune time for the presentation of this study only about 7000 histories were analyzed. In 6968 families there were 27,711 pregnancies including miscarriages and stillbirths, an average of 3.9 per family. Of these 27,711 pregnancies 2239 were miscarriages and 413 were stillbirths, the remainder, 25,059 represented the number of living births, or 3.6 live-born children to each family. The total number of deaths under one year of age of living births was

3232. From the first to the eighth year there were 1081 additional deaths, or a total of 4313 deaths of living births. Including miscarriages and stillbirths the total number of deaths up to eight years was 6965 in the 27,711 pregnancies or 25 per cent. Computed in terms of per thousand pregnancies the miscarriage rate was 80.7 per thousand, and of all living births was 89.3 per thousand. The infant death-rate up to one year of age was 128 per thousand living births. In contrast it is of interest to note that the death-rate in the same age group was 70 per thousand of the children who were under the care of the clinic. The child death-rate (up to eight years) reached 172 per thousand.

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**Acute General Peritonitis in Infants.**—Boss (*Pennsylvania State Med. Jour.*, March, 1920) reports four cases, two of which were males and two were females. The ages were four weeks, eight weeks, three weeks and four months respectively. Only one case was characterized by persistent vomiting. Neither diarrhea nor constipation were prominent features. All had some elevation of temperature, which was high at the onset. Cyanosis was present in one case and great depression was present in all. The symptom common to all was marked distention of the abdomen with general abdominal tenderness. In all four the peritonitis seemed to be a part of a general septicemia complicating infectious processes elsewhere in the body.

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**Studies with a New Method of Determining the Coagulation Time of the Blood in the Newborn.**—RODDA (*Am. Jour. Dis. Children*, April, 1920) describes a method in which the apparatus consists of a spring lancet or scalpel, two one and a half inch watch-glasses and a No. 6 lead shot. The first step consists of cleansing the glasses and shot with soap and water followed by alcohol and ether. The lance should be sterile. The finger of the infant is sponged with ether, and a puncture is made to produce free flow of blood without pressure. A clean watch-glass containing a No. 6 shot receives the second drop of blood. The second watch-glass is inverted over the first. They are tilted every thirty seconds until the shot no longer rolls, but is firmly imbedded in the clot. The time is reckoned from the falling of the first drop until the shot is firmly fixed in the clot. Determinations are made to the nearest half minute. This method has the advantage of being simple, easily applied in the newborn, and gives results more accurate than those obtained with the Lee and White method. The average coagulation time in the newborn with this method is seven minutes, with a normal average of between five and nine or ten minutes. The average bleeding time in the newborn with Duke's method is three and a half minutes with a normal range of from two to five minutes. In the normal newborn there is found a tendency to prolongation of these times in the first days of life. Hemorrhage is accompanied in many cases with an exaggeration of the tendency or markedly prolonged coagulation and bleeding time. The coagulation and bleeding time should be studied in conjunction. Routine determination in the newborn will allow the selection of at least certain of the hemorrhagic conditions before the onset of symptoms, and give the indication for the administration of blood. The method will allow for a check on blood therapy in hemorrhages of the newborn.

## OBSTETRICS

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UNDER THE CHARGE OF

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**The Retention of Urea in Disease of the Kidney.**—SCHLOTZ (*Norsk Magazin*, April, 1919, No. 4) describes three cases of detachment of the retina in pregnant women who had nephritis. Each patient was a primipara, one seventeen, one twenty-nine and one thirty-five years old. Each had albuminuria and eclampsia, but without marked edemia. They were all emmetrope and detachment of the retina occurred after several convulsions, in the older woman in both eyes. In this case, the accident happened at the seventh month and persisted for a month after the patient had premature labor. The retina finally returned to its place, with considerable division. In this woman, during a second pregnancy, albuminuria returned five years later; but disappeared at spontaneous premature labor, at seven months. At this time, vision was not affected. In the second patient, there was retinitis and detachment of the retina, which lasted until delivery, at seven months, in all about two weeks. Finally, the retina returned to its place, and in two days, there was no trace of the detachment. The younger of the three patients developed eclampsia, after full-term delivery, and detachment of the retina occurred, without any signs of retinitis. In this woman, the detachment has persisted for a year. The fourth was that of a myopic woman, in her fourth pregnancy, who had detachment of the retina. The affected eye became totally blind and, in the other, detachment of the retina occurred just before term, in the fifth pregnancy. There was no trace of sugar or albumin in the urine. Operation was done on the eye just before delivery and, within a week, the retina had returned to place but vision was much affected, and grew worse after a few months. The writer knows of only four similar cases of detachment of the retina in pregnant women, without albumin in the urine, and of the five total cases, three were strongly myopic. The detachment persisted unmodified in all but one case. In two of the others, the retina in the other eye became detached at the fourth or the sixth month, in a later pregnancy. In both cases, artificial delivery at once was followed by restoration to place of the retina and the gaining of vision. It is clearly shown that the longer the time between the detachment of the retina and the delivery of the child, the smaller is the chance of the retina going back to place. Accordingly, when this accident happens, pregnancy should be terminated at the earliest possible moment.

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**Coexistent Disease of the Appendix and Pelvic Organs in the Female.**—CHILD (*Am. Jour. Obst.*, July, 1919) studied the relation between disease of the appendix and pelvic disease in the female in 748 operative cases. In 746 the appendix was removed 339 times, it was physiological 244 times, a percentage of 32.57 for the whole series. When there was

an inflammatory condition of the tubes or ovaries the average was 46.70 per cent., if the inflammation was limited to the right broad ligament 66.66 per cent. had involvement of the appendix, and when the inflammation was on the left side or the uterus but 18.42 per cent. of cases had disease of the appendix. When both tubes and ovaries were involved, 38.38 per cent. In all cases of inflammation of the right tube or ovary the appendix was involved 43.95 per cent. and appendix actually adherent to the adnexa on the right side in 19.09 per cent. Among these cases there were 99 in which the appendix was removed at the request of the patient but microscopic examination failed to find disease. There was marked atrophy of the appendix in 10 cases and then it was not removed. The appendix was found in the pelvis adherent to a diseased right tube or ovary in 75 cases in which 25 showed acute inflammatory changes while 37 were subacute or chronic. One of the most interesting cases in the whole series was that of right tubal ovarian abscess with adherent appendix, where the lumen of the appendix connected directly with the abscessed cavity. The infection in this case was by the colon bacillus. In another patient the pyosalpinx had ruptured spontaneously through the abdominal wall, a sinus thus made communicated with the uterine cavity through the tube and the patient menstruated regularly each month through this sinus. At operation a chronically inflamed appendix four inches long was found also adherent to the abdominal wall and fused to the tube by dense adhesions. A cystic appendix filled with gelatinous material and measuring 6.5 cm. in length was found in 1 case. The author concludes that disease of the pelvic organs in the female is an important exciting cause of appendicitis and that to a lesser extent inflammation of the appendix may cause disease in the right Fallopian tube. He believes that the primary source of infection is more often in the pelvic organs than in the appendix. When this inflammation is on the right side of the pelvis, the appendix is involved four times more frequently than when on the left. It follows that when operating one should always remember that both pelvic organs and appendix should be inspected. The appendix should be removed if possible whenever the abdomen is opened. The author goes to the extent of saying that appendicitis in the female is associated so frequently with pelvic disease that it should be considered a gynecological condition. Obstetricians are interested directly in inflammation of the appendix as it frequently complicates pregnancy and the puerperal state. It is not, however, a frequent complication of puerperal septic infection and hence if the statements of the author quoted are correct, non-puerperal inflammation of the pelvic organs must be the most frequent cause of appendicitis in the female. The circumstances in pregnancy are peculiarly favorable for the development of the colon bacillus and such has most usually been found to be the cause.

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**Report of a Case of Full Term Ectopic Pregnancy.**—RAWLS (*Am. Jour. Obst.*, July, 1919) reports the case of a primipara, aged nineteen years, seen in the twenty-second week of her pregnancy. At six weeks a catheter or sound had been introduced, which caused bleeding for several days; it was thought that abortion had been accomplished until a few days before coming to hospital, when the patient's abdomen suddenly enlarged. On admission the fundus was above the umbilicus,

a placental bruit could be distinctly heard and it was thought pregnancy was further advanced than the history indicated. The patient then passed from observation until five months later. She had been well until the previous week, when she was attacked with pain over the gall-bladder, with nausea, vomiting, constipation and voiding small quantities of highly colored urine. The patient was slightly jaundiced and was treated by catharsis, diet and colon irrigation without improvement. When admitted to hospital temperature was  $101^{\circ}$ , pulse 144 (weak and irregular), respiration 30 and difficult. On palpation a firm tumor mass could be felt extending from upper left quadrant to the umbilicus. There was well marked dullness in the flank on the left side, just below the umbilicus could be heard a fetal heart and below this the placental bruit. On vaginal examination the cervix was displaced to the left, the external os admitted finger only to the internal os, behind the cervix was a cystic mass with indefinite firmer mass above on the right and below the level of the internal os. There was there a small hard mass which suggested some part of the child. The patient was thought to be at full term with natural intra-uterine pregnancy complicated by toxemia, with either incomplete rupture of the uterus or an ovarian cyst with twisted pedicle. The patient improved after admission to the hospital, but the fetal heart sounds ceased and no fetal movements were observed. The patient continued to improve, the urine grew better, blood analysis showed carbon dioxide in the blood 23 with marked reduction in urea. On the sixth day after admission abdominal section was performed, there was considerable vaginal bleeding from preparation and examination and the vagina was packed with gauze. A sound was not passed into the uterus. When the peritoneum was opened there was a gush of bloody serum. The fetus was found with head toward the left of the sternum showing distinctly through a thin sac, this sac was thicker posteriorly and adherent at intervals to the omentum, large intestines and peritoneum. The pedicle was in the region of the left broad ligament. The membrane was then opened and amniotic fluid and child removed. On separating the adhesions the pedicle was at the site of the left tube and the upper part of the broad ligament above the ovary and extended to the uterine horn but did not involve the fundus of the uterus. The pedicle was firmly secured and the placenta and membrane removed with very little loss of blood. The uterus was the size of a four months pregnancy and had been carried backward, upward and to the left. The pedicle was secured with ligatures and sutures and portions of the membrane were removed from the omentum, intestines and peritoneum, the abdomen was closed without drain. The patient made an uneventful recovery and was convalescent in two weeks. The child was at term and macerated.

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**Labor Complicated by Breech Presentation with Fetus in Hyperextension.**—LAFFONT (*Arch. mens. d'obst. et de gyn.*, February, 1919) reports the case of a primipara, aged thirty years, admitted to the hospital in labor with breech presentation. The membranes ruptured spontaneously and a large quantity of amniotic liquid escaped. When dilatation was complete a foot of the child appeared at the vulva, the head descended into the pelvic excavation and about half hour afterward a male child, weighing 2780 gm. was born in a condition of appar-

ent death. The child was finally resuscitated but breathed very badly. It was found in a condition of hyperextension and this is well illustrated by a photograph of the infant. An autopsy was performed and the spinal cord of the child exposed, from the border of the seventh cervical vertebra to the first dorsal vertebra the spinal cord was bare, the meninges terminated in the skin at a point where the roots of the seventh pair of cervical, down to the eighth pair of cervical nerves had issued from the cord. The seventh pair of cervical nerves was denuded, deprived of its envelope of membrane and the left branch was disintegrated. The eighth pair was not denuded but one observed that this nerve proceeded obliquely. On opening the membrane of the cord it was found that there had been a hemorrhage into the arachnoidean space. This extravasation of blood or hemorrhage had great effect through its pressure upon the functions of the cord. The rupture of the membranes of the cord had evidently been caused by condition of hyperextension of the head upon the trunk during the course of fetal development. Examination by roentgen ray failed to find any bony lesions. The Wassermann reaction in the mother was negative. The author quotes Bar's case, in which the cranium was markedly dolichocephalic.

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**Influenza and Pregnancy and the Puerperal Period.**—CALDERON (*Jour. Am. Med. Assn.*, September 27, 1919) reports 36 cases of influenza in parturient women of which 9 occurred in the puerperal period. It was found that among pregnancy patients, independently of bronchopneumonia or lobar pneumonia, that influenza exerted a very pernicious influence. In patients who were not pregnant it caused menstruation to appear at unnatural periods. The great element of mortality in these cases was lobar pneumonia during pregnancy, while in the puerperal period bronchopneumonia was the cause of death. Among the infants there were seven deaths, including intra-uterine deaths and there was 1 case in which the temperature of the newborn child rose very high.

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**Interstitial Pregnancy.**—VAUDESCAL (*Arch. mens. de obst. et de gynec.*, April, 1919) described a remarkable case of interstitial pregnancy which continued for more than four months without serious accidents from pressure. The placenta in the original implantation cavity of the ovum continued to develop, while the fetus was encysted. In this and another similar case the operation consisted in removing the uterus. In the third case an emergency section was done for hemorrhage and a wedge-shaped reaction was performed. From a study of this and other cases we may conclude that interstitial pregnancy develops like other ectopic gestation and also ruptures in a similar way. In diagnosis the lack of symmetry in the adnexa is significant and also the fact that on the affected side the round ligament is inserted at the site of the tumor. Tubal pregnancies are usually found more posterior toward Douglas' cul-de-sac. Where the ectopic gestation is anterior the development of the case will usually make the diagnosis clear. It must not be forgotten that the ovum sometimes passes into the uterine cavity when it has originally been located in the angle of the uterus. If, however, it is a genuine interstitial pregnancy it proceeds to rupture. Although careful search was made there was no evidence that decidua were produced in these cases.

## GYNECOLOGY

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**Treatment of Uterine Cancer.**—TAYLOR (*New York State Jour. Med.*, 1920, xx, 8) very properly divides the treatment of uterine cancer into four parts, namely, publicity and education, prophylaxis, treatment of operable cases and treatment of inoperable cases. The importance of publicity, education and prophylaxis needs no further discussion in a brief abstract of this kind, therefore we shall confine our attention to his views on the treatment of cancer after the diagnosis has been made. Our definition of an operable case is frequently changed. A few years ago, before radium was in common use, many cases were considered operable that would now be placed in the inoperable class. Formerly, we knew that if a case was not operated upon there was no hope; therefore, we were led to operate on many cases in which the chance of cure was comparatively small and the risk of the operation correspondingly great. With the use of radium, however, the case is not necessarily hopeless without operation, and even if not permanently cured, life can be prolonged and the patient given great comfort by its use. The use of radium, however, has developed another class of cases, that is, the cases which were inoperable before treatment, but as the result of the use of radium become operable. In the treatment of operable cases, that is, cases in which the growth is limited to the uterus, with possibly a limited superficial involvement of the vaginal walls, Taylor believes that a combination of radium and operation offers the greatest hope of a permanent cure. It is his custom in such cases to make an application of radium, usually 100 mg. for twenty-four hours, and then after a few days, usually less than a week, to allow the possible reaction from the radium to subside, to do such abdominal hysterectomy as the case indicates. If the case is favorable he does a radical abdominal hysterectomy, with the isolation of the ureters and the removal of the pelvic connective tissue as far as possible. If the case is more difficult on account of a thick abdominal wall or any concurrent constitutional disease he would be satisfied with a simple hysterectomy. It has been stated that a hysterectomy after the use of radium is associated with greater difficulty on account of increased liability to hemorrhage and to the absence of the usual planes of cleavage. It has not been Taylor's experience that the increased difficulty has been sufficient to contra-indicate an operation following the use of radium; there may be some increased bleeding, but in no case has this been difficult to control. There is usually some edema about the bladder fold and at the bases of the



broad ligaments, but this has never interfered materially with the operation nor with the subsequent healing of the wound in any of his cases. Following the operation, and previous to the patient's discharge from the hospital, that is, at the end of three or four weeks, an application of radium to the top of the vagina is made. There are, of course, cases which are so far advanced that it would be folly to do anything other than to use morphin for the relief of pain and discomfort and proper douches for cleanliness. In these cases the possibility of causing irritation to the bladder or rectum, associated with additional discomfort, is such that the cases are more comfortable without any local applications of radium. Excluding these advanced hopeless cases, there has been nothing in Taylor's experience in the treatment of inoperable cancer of the cervix that has approached the use of radium in its results. It has advantages over the use of the cautery in that it can be applied without an anesthetic, with practically no discomfort to the patient; it requires but a short stay in the hospital, and the results are often striking. The treatment of the inoperable case that has changed into the operable class by the use of radium is open to various opinions. Taylor would be willing to take a considerably increased primary risk if by doing so there is a correspondingly increased chance of a permanent cure; in fact, it is his custom, if the case is a good operable risk, to do either a simple or a modified radical hysterectomy.

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**Ectopic Adenomyomata of Uterine Type.**—Of Clinical as well as pathological interest are the ten cases reported by MAHLE and MAC-CARTY (*Jour. Lab. and Clin. Med.*, 1920, v, 218), representing extra-uterine and extratubal tumors, which were diagnosed at the time of operation as adenomyomata. These growths contained glandular portions resembling typical uterine mucosa, surrounded by a fibrous connective tissue and smooth muscle stroma, the latter in varying amounts. The distribution of the tumors was as follows: Umbilicus, 1; abdominal wall, 2; sigmoid, 1; groin, 2 and rectovaginal septum, 4. They point out that, pathologically, extra-uterine adenomyomata are identical in appearance regardless of where they are found. They differ grossly from adenomyoma of the uterus, in that the cystic areas are larger and the contents darker brown. Grossly the tumors are solid, fibrous and of a light gray color. Here and there white bands extend into the tumor substance, while between these bands are areas, dark brown to almost black, varying in size from the head of a pin to cystic areas 1 cm. or more in diameter. On pressure a dark brown fluid exudes from the larger areas. Clinically, these tumors give no consistent group of symptoms on which an accurate diagnosis can be made. However, their location and their slow growth, extending over a period of years, suggests benign tumors. Further, the occasional relation to the time of menstruation, of pain or swelling of the tumor, or less frequently a bloody discharge, should be very suggestive of adenomyoma. Surgically, these tumors, regardless of their remarkable infiltrative characteristics, should be differentiated from malignancy. Especially is this true of tumors in the pelvis, adherent to the sigmoid or the abdominal wall or other structures. Adenomyomata may be recognized grossly in most cases by the fibrous

stroma, which contains cystic areas filled with a bloody, dark brown or serous fluid. The pathologist should distinguish adenomyoma from carcinoma by the regularity of gland structure with normal differentiated epithelial cells without mitoses, and, in most tumors, by the characteristic stroma surrounding the gland. He should also recognize that they are benign tumors, that they grow by invasion and do not metastasize. All of the cases here reported occurred in patients between the ages of twenty-nine and fifty years and pregnancy apparently had no influence, for 6 of the cases occurred in nulliparous women. Of the 10 patients 6 gave a history directly referable to the tumor; one stated that a tumor mass was found during operation elsewhere, for other symptoms of which the patient complained at that time. The remaining three patients had adenomyomata of the rectovaginal septum, which were so small that they were giving no trouble. In these cases the symptoms, when they were noted in the history, were enlargement, pain in the rectum or vagina at the time of menstruation, or a vaginal discharge.

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**Roentgenotherapy of Fibroids.**—The results obtained in 400 cases of uterine fibroids that were personally observed while undergoing treatment by means of the roentgen ray is the basis of a communication from BECLERE (*Arch. Radiol. and Electrother.*, 1920, xxiv, 254). Of these patients approximately 25 per cent. were over fifty years old while about 11 per cent. were under forty years, so that the largest group (64 per cent.) were between forty and forty-nine years old. Concerning the size of the tumors subjected to treatment, he states that 85 per cent. of the tumors were palpable through the abdomen before treatment. His technic consists of weekly seances each of which consists of two successive radiations, the one to the right, the other to the left of the median line of the abdomen, immediately above the horizontal rami of the pubis. Occasionally, when the uterus is retroflexed, when the fibroid occupies the cavity of the sacrum or the neck of the uterus, a third radiation is directed on the sacral region. Finally, if the dimensions of the tumor demand it, the surface of the abdomen is divided not only into two, but into three, four and up to six circular areas, which in turn, serve as portals of entry for the rays. Each irradiation is localized to a circular surface of 10 cm. in diameter, by the aid of a cylinder of lead glass opaque to roentgen rays. A thin disk of wood is interposed between the localizing cylinder and the abdominal wall which depresses, levels the surface, and distributes over a considerable area the weight of the cylinder, and serves by a gentle compression, to reduce the distance between the ovaries and the skin. In 60 per cent. of the cases, the treatment has not required more than twelve to fourteen of these weekly seances, and has not lasted more than two and a half to three months. In only 4 cases has the treatment failed to avoid surgical treatment for the hemorrhage, while in the majority of cases the periods were suppressed without having appeared more than two or three times after the start of the treatment. This menopause, prematurely provoked, was usually definitely established, although in 12 per cent. of the cases, the suppression of the periods was only temporary and the periods returned after several months or years. In these cases further treat-

ment restored the menopause. In every case treated, not only was the growth of the tumor arrested but its size was diminished. Beclere firmly believes that the rays act directly on the fibroids, arresting their development and leading to a reduction in their size. He has found the treatment as efficacious before as after forty years of age and that it can be applied with equal success on either large or small tumors.

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**Relation of Pregnancy to Tumor Growth.**—Having handled large numbers of mice with spontaneous tumors, SLYE (*Jour. Cancer Research*, 1920, v, 25) at once observed the great difference in the rate of tumor growth in the non-reproducing and in the reproducing females and she states that this same difference is noted in the rate of tumor growth in the non-reproductive and in the reproductive periods of the same female. In order to investigate this problem, thirty each of non-reproducing and of reproducing females with spontaneous tumors were selected. The tumors were all of the same type and of the same organ, viz., alveolar tubular carcinoma of the mammary gland, of which a daily observation is easily made. Without exception, the amount of tumor grown by a female while reproductive was strikingly less than during her non-reproductive period. Again, the amount of tumor grown by reproducing females was strikingly less than that grown by non-reproducing females. The normal course of these spontaneous tumors in mice that are not bred is very rapid, the mouse rarely living over six weeks and often less than a month after the appearance of her tumor. The tumors grow to a great size, frequently being as large as the body of the mouse. When, however, these tumorous mice are bred, the tumor scarcely grows at all during the reproductive period. The duration of the tumor is greatly prolonged, the mice frequently living nearly a year after the appearance of their tumors, during which time many bear from six to eight litters aggregating from twenty to thirty two young. When the mouse ceases reproducing, the tumors grow with tremendous rapidity and to great size, the female frequently surviving only six or eight days after the birth of the last litter. During this brief period the tumor grows to many times its size at the date of the last litter. In brief, during the six or eight days a mouse is non-reproductive, she grows enormously more tumor than during the eight months or a year while she is reproductive. From these observations, Slys concludes that cancer and reproduction, both being growth processes, draw upon the same energy residuum and are made possible by the same food, hence the food and energy used by one are withheld from the other. Therefore, if the female is constantly pregnant, energy and food are withheld from the tumor and it grows with extreme slowness. If there is a hiatus between pregnancies, or a termination of pregnancy, the energy which was running into reproduction is released and diverted into tumor which grows very rapidly. If tumor growth considerably antedates impregnation, the currents of energy are already being used for tumor growth and are with difficulty diverted for pregnancy, probably never wholly so. Hence when a female is well advanced in tumor growth before impregnation there are rarely any offspring brought to birth. When offspring are delivered, they are few, small, undernourished and rarely suckled.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**Ultraviolet Spectroscopic Studies of Blood Serum.**—In a physicochemical study of blood serum, TADOKORO (*Jour. Infect. Dis.*, 1920, xxvi, 1) shows that the antagonistic action of two salts, viz.,  $\text{CaCl}_2$  and  $\text{NaCl}$ ,  $\text{ZnSO}_4$  and  $\text{CaCl}_2$  and  $\text{ZnSO}_4$  and  $\text{NaCl}$  is due to the changes which they bring about in the colloidal state of the constituents of the serum. Examination of normal serum with the ultraviolet spectroscope and the ultramicroscope showed that the presence of mikrons possessing Brownian movement was associated with a definite absorption band in the ultra-violet. When the serum was mixed with  $\text{ZnSO}_4$  or  $\text{CaCl}_2$  its particles formed aggregates and became heterogeneous. Photographs of the spectra of these sera then showed that the absorption band tended to move away from the ultra-violet end of the spectrum. Addition of the second salt, *e. g.*,  $\text{NaCl}$  caused the aggregated particles to become free and homogeneous as in the normal serum. That is, the dispersion of the particles had been reversed and when this reversion occurred it was observed that the absorption band then moved toward the shorter wave length, or ultra-violet end of the spectrum. It is interesting to note that Tadokoro's conclusion that the antagonistic action of salts finds its explanation in changes in the degree of the dispersion of the colloidal particles confirms Clowes' interpretation of the same phenomenon, though the later investigator obtained his results mainly by means of surface tension measurements. In conjunction with NAKAYAMA, the author (*Ibid.*, p. 8) used the same method to investigate the changes produced in the colloidal state by immunization. Differences in the normal sera of the dog, guinea-pig, rabbit and horse were indicated by the fact that a similar absorption band, viz., between wave lengths 2950 and 2400 mikrons, could only be obtained by varying the dilution of each. When immunization was effected in these animals, comparison of the ultraviolet spectrographs of the serum of each showed that the width and intensity of the absorption band in the immune serum were always greater than those found in the normal serum.

**Dairy Infection with Streptococcus Epidemicus.**—BROWN and ORCUTT (*Jour. Exper. Med.*, 1920, xxxi, 49) report a milk-borne streptococcus epidemic occurring during February, 1917, at Boston. The malady, which was most prevalent in children, began as a moderately severe sore-throat, attended by submaxillary and cervical lymphadenitis. A few cases experienced a peculiar nauseating nasopharyngitis, as well as otitis media. Recovery was sometimes quite slow and characterized by recurrent periods of high temperature. A very similar organism was isolated from the throats, tonsils and ears of the afflicted, from one cow in a herd of 112 and from eight of twenty-six employees of the dairy

These strains, isolated on 80 occasions, could not be distinguished morphologically nor biologically from one another. Cultures from adults in the families where the children were ill and from other cases of epidemic adenitis, not using the milk from this dairy, failed to reveal the presence of the *Streptococcus epidemicus*. The positive cultures from the cow were obtained from the udder. These appeared before the milk was grossly infected. The authors again emphasize the fact that infection of the cow's udder by *Streptococcus epidemicus* may persist for some time without gross evidence of mastitis and that the relative rarity of such milk-borne epidemics can be explained by the theory of Smith and Brown, in that streptococci of human, not bovine, origin are at fault. *Streptococcus epidemicus* in the blood agar plate, produces the beta type of hemolysis, similar to that of *Streptococcus pyogenes*, but usually slower in developing. The organism exhibits capsules in fresh surface colonies, where it resembles the growth of *pneumococcus mucosus* (type III), except that the latter produces the alpha appearance in blood agar. Although the organism was not particularly fatal to rabbits, an erysipelatous condition of the ears and an orchitis were the most conspicuous lesions. The epidemic ended immediately upon pasteurizing the milk and later, eliminating the affected cow from the herd. It is recommended as a minimum requirement for dairies producing raw milk that a regular examination of throat swabs from milkers and blood agar rather than plain agar for milk counts be employed.

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**A Method of Standardizing Bacterial Suspensions.**—Many methods of determining the concentration of bacterial suspensions have been advocated. The more accurate methods involve much time and labor, while the simpler ones give only a rough approximation of the bacterial count. GATES (*Jour. Exp. Med.*, 1920, xxxi, 105) points out that if a wire loop is gradually introduced into a suspension of organisms in a test-tube and viewed by looking down into the tube through its mouth the depth at which the loop disappears will be determined by the opacity of the supervening column of the suspension. Experience has shown that, with a little practice, the depth of disappearance of the loop can be read within 1 mm., an error of less than 10 per cent.; nor, within certain limits, does the diameter of the test-tube nor the size of the wire loop affect the readings appreciably. The determination of the relation of the depth of disappearance to the concentration will give a quick and simple method of standardizing bacterial suspensions with a minimum of apparatus and manipulation. If a given suspension causes the loop to disappear at a given depth, in a dilution which is just half as heavy, the loop will not disappear at twice the distance, but at a point less than twice the distance. This discrepancy is due to the presence of a constant which is a function of the size and opacity of the individual bacteria in suspension. While the constant is the same for any series of readings on the same suspension, it varies with each suspension examined. The problem is to eliminate the constant, thereby bringing opacity and concentration into accord. Each of the observed readings on a single suspension is the sum of the corrected reading and the constant. The corrected reading for any suspension, by which its concentration may be compared with that of a standard suspension of the same organism, may be found by making a reading on the suspen-

sion, adding an equal amount of diluent, making a second reading and subtracting the first reading from the second. The higher the suspension is diluted, however, the less the error of observation. If a permanent standard is desirable which is then translated into terms of an accepted standard as the weight of dried bacterial substance on the number of organisms per c.c. the number of bacteria in any suspension can be found by inverse proportions. The apparatus can be very simple, consisting of a loop of nichrome wire thrust through a cork and measured with a centimeter scale laid against the test-tube. Another instrument is described by the author, who believes the method should be useful in the standardization of bacterial suspensions.

**The Cultural Differentiation of Beta Hemolytic Streptococci of Human and Bovine Origin.**—Although many good dairy products contain harmless hemolytic streptococci, it is of advantage to be able to identify those strains of hemolytic streptococci which are pathogenic for man. As no qualitative method for distinguishing hemolytic streptococci of human and bovine origin has been described, our ability to differentiate them has depended upon such quantitative reactions as agglutination and precipitation titer, the rapidity of hemolysis, the appearance of the colony in the blood agar plate, the rate of coagulability of milk and the action of a bouillon culture on blood corpuscles in suspension. BROWN (*Jour. Exp. Med.*, 1920, xxxi, 35) emphasizes the differential value of the action of streptococci of human and bovine origin on blood corpuscles in fluid media. Observations were made on twenty-eight carefully selected strains of bovine and human origin. The technic recommended by the Medical Department of the U. S. Army in 1918 for the identification of *Streptococcus hemolyticus* and a slightly different method of the author were employed with practically the same results. The latter consisted of diluting eighteen- to twenty-hour standard meal or beef infusion bouillon cultures to twenty times its volume with sterile 0.85 per cent. salt solution. One drop of sterile defibrinated horse, human, rabbit or beef blood is added to 1 c.c. of the diluted culture and incubated at 37° C. for two hours in the water-bath. As the test is purely quantitative, dilutions must be accurate. It was found that the strains of human origin hemolyzed the blood cells, while those of bovine origin did not and that the reaction depends upon the dilution of the medium rather than the dilution of the bacterial suspension. As a rule, in the blood agar plate, the bovine strains appeared as a small, clear, sharply defined central zone and a broad, outer, partly hemolyzed zone, some developing more slowly than the human strains which gave a clear, colorless, well-defined, completely hemolyzed wider zone of hemolysis. The pathogenic human strains of the beta type are of uniform size and character, whereas the bovine strains showed considerable variation. In some cases, however, it is very difficult to state positively the origin of the colony by its appearance in the blood agar plate. The titrable acidity after incubation for one week of the twenty-eight strains in bouillon plus 5 per cent. sterile horse serum and 1 per cent. saccharose, lactose, salicin, raffinose, inulin and mannite gave no characteristic reactions. The limiting hydrogen ion concentration of cultures in 1 per cent. dextrose bouillon after incubation of sixty-eight hours showed, as a rule, a higher reading with the human strains than the bovine. In milk, none of the human strains caused coagulation

within twenty-four hours, while about 50 per cent. of the bovine strains did. The findings of Sherman and Albus, that cultures of *Streptococcus lacticus* reduce methylene blue in milk while those of *Streptococcus pyogenes* fail not only to do so but also to grow in this medium could not be confirmed in all instances and doubt as to the validity of selecting cultures by these workers is expressed. Of the twenty-eight strains, five were defined as irregular, the rest easily falling into the human or bovine groups. The author concludes that none of the procedures described serves by itself to differentiate streptococci of human or bovine origin with certainty, though each of them serves as a strong presumptive test.

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**Fungous Developmental Growth Forms of *Bacillus Influenza*.**—The causative agent of epidemic influenza and the exact role of Pfeiffer's *Bacillus influenzae* in this disease seems still far from solution. Recently, some investigators report success in their search for a filtrable virus. It would appear possible since familiar organisms, of supposedly fixed morphology, may assume a filtrable phase that this might be applicable to *Bacillus influenzae*, and, for this reason, the morphologic stability of the organism is important. With these ends in view, WADE and MANALANG (*Jour. Exp. Med.*, 1920, xxxi, 95) attempted to determine the essential factors influencing the pathogenicity of certain strains of influenza bacilli obtained at autopsies and noted the familiar bacillus in but a simple form of an organism capable of complex development. Three strains were investigated, all of which failed to grow in the absence of hemoglobin. The optimum growth was on hot mixed (80°–90° C.) blood agar. One strain showed short, plump forms, while the other two tended to be longer. The pathogenicity to monkeys was lower than when first isolated. Toxin production was tested only for the first strain. The media consisted of beef infusion bouillon with Witte's peptone and sodium chloride to which was added laked or heated sheep or horse blood. Seeding was done by inoculating 0.1 to 0.2 c.c. of a saline suspension from a twelve- to twenty-four-hour agar growth into an ordinary tube culture. It was found that the bacilli abandoned their usual form and grew as a frank fungus of the *Discomyces* type. One strain yielded little of the filamentous growth in the cultures, but spore-like bodies which are structurally delicate were produced. These were, as a rule, greatly injured in ordinary preparations and were best demonstrated in Congo-red films. Conidial bodies, particularly when grown in symbiosis with streptococci, were abundant and apparently developed by direct transformation from short bacillary elements, as terminal knobs on simple rods or on short branches that might be likened to conidiophores, or as simple lateral buds. When grown with pneumococcus the bacilli disappeared in a few days. Though the original cultures were not dead, repeated subplants on blood agar from fluid cultures remained sterile, suggesting that the described forms are not due to involution but are the result of an adaptation to influences in the medium. Distinct stages in the depression of cultivability occur. A few attempts to perpetuate the fungous growth in the fluid media were made but subcultures have not developed to any great extent. The authors feel that they were working with pure strains of true influenza bacilli.

## HYGIENE AND PUBLIC HEALTH

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**A Possible Mechanism for the Excitation of Infections of the Pharynx and Tonsils.**—The vasomotor reactions of the buccal and pharyngeal mucous membranes to chilling of the body surface have been studied by MUDD and GRANT (*Jour. Med. Research*, 1919, xl, 53–101) in the hope of throwing light upon the mechanism by which chilling may excite infection of the mucous membranes by their indigenous bacteria. The authors devised simple wire “applicators” for holding in apposition with the skin or exposed mucous surfaces the terminals of thermopiles in circuit with a d’Arsonval galvanometer. From the thermometer and galvanometer readings the temperature of the surfaces beneath the thermopiles may be computed and temperature changes accurately followed. The cutaneous chilling of these experiments caused only inconsequential changes in blood temperature and pressure. Rate and depth of respiration were kept constant. Superficial temperature varied directly with rate of blood supply, and was an index of local vasomotor tone. This thermogalvanometric method, checked by observations of color change, showed that chilling of the body surface causes reflex vasoconstriction and ischemia—not, as hitherto assumed, congestion—in the mucous membranes of the palate, faucial tonsils, oropharynx and nasopharynx. With inhalation of amyl nitrite, skin temperature has always shown a sharp, transient rise. The mucous membranes, if relatively ischemic, show a rise parallel to the skin. If already hyperemic, local vasodilatation in the mucous membrane with amyl nitrite is more than counterbalanced by the lowering of general blood-pressure and the temperature falls. Scar tissue showed reflex vasoconstriction parallel to that of the neighboring skin. The earliest scar tested and proved to have vasomotor fibers was at the site of an operation performed a month before for removal of a keloid. In four instances exposure was followed by a “cold” or sore-throat. It does not seem improbable that the ischemia of the mucous membranes incident upon cutaneous chilling might so disturb the equilibrium between the host and the bacteria in the tonsillar crypts and folds of the pharyngeal mucosa as to excite infection.

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**Influenza at San Quentin Prison, California.**—STANLEY (*Public Health Reports*, 1919, xxxiv, 996) reports three distinct epidemics of influenza in 1918, the first in April with 500 cases, the second in October with 69 cases, and the third in November with 59 cases. The mode of



conveyance was believed to be rather direct contact and it was thought that moving picture shows were responsible for considerable extension of the epidemic. Masking was tried, but appeared to have no influence on the spread of the infections. Tuberculosis developed in a number of cases. The following conclusions are drawn: (1) Each epidemic was apparently introduced by a recently infected entrant. (2) Close contact in crowded, poorly ventilated showrooms probably spread the infection. (3) The incubation period is from forty to sixty hours. (4) The second epidemic was less severe than the first, and the third less severe than the second, as shown by the number diseased, number of pneumonia cases, and number of deaths in each. (5) The infection spread in definite groups by close contact, as shown by its course in the rooms where night school was held. (6) The disease in the first and second epidemics attacked more prisoners between ages twenty to twenty-five, but in the third, more between the ages twenty-five and thirty as well as forty to forty-five became ill. (7) The most effective means available for combating the spread of the disease in this prison were hospitalization, quarantine, isolation, and closure of congregating places. (8) From the first epidemic it is seen that 5 per cent. developed tuberculosis. (9) It appears that those men who entered prison after the April epidemic were attacked in greater numbers than those who had come before, although there were more of the latter than the former.

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**The Surgical Treatment of Typhoid Carriers.**—NICHOLS, SIMMONS and STIMMEL (*Jour. Am. Med. Assn.*, 1919, lxxiii, 680-684) believe that the so-called urinary typhoid carriers are really kidney carriers, and can be cured by nephrectomy; that intestinal carriers are really bile passage carriers of two kinds, (a) cases in which the gall-bladder alone is infected and which can be cured by cholecystectomy, and (b) cases in which gall-bladder and bile passages are both infected, and which cannot be cured by surgical measures.

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**A Study of the Relation of Diet to Pellagra Incidence in Seven Textile-mill Communities of South Carolina in 1916.**—GOLBERGER and WHEELER (*Public Health Reports*, March 19, 1920, pp. 648-708), to supplement their studies, chiefly experimental, of 1914 and 1915, began a study in the spring of 1916 in seven cotton-mill villages of South Carolina of the relation of factors of a dietary, economic and sanitary character to the incidence of pellagra. In this report they give the results of the first year's work with respect to the relation of household diet to pellagra incidence. They state that the selected communities were typical cotton-mill "villages," and were of about average size; none had over 800 or less than 500 inhabitants. Only the families of white mill operatives were included in the study. Pellagra incidence was determined by a systematic biweekly house-to-house search for cases carried on continuously from April 15, 1916, to the end of that year. Only patients with a clearly defined bilaterally symmetrical eruption were recorded as having pellagra. It is suggested that, clinically, pellagra includes at least two commonly associated but etiologically essentially distinct, though closely related, syndromes. The indications afforded by this study suggest that the pellagra preventive power of a milk or a meat supplement is due to the effect of a correction in the type of diet studied, of a deficiency supply either (1) of some

amino-acid or acids, (2) of the ash or of some of its constituents, (3) of some as yet unknown essential (vitamine?) or (4) of all or of a combination or combinations of some of these. Conversely, they suggest that the pellagra-producing dietary fault is the result of some one or of a combination or combinations of two or more of the following factors: (1) A physiologically defective protein (amino-acid) supply; (2) a defective or inadequate mineral supply; (3) a deficiency in an as yet unknown dietary essential (vitamine?). The somewhat lower plane of supply, both of potential energy and of protein, in the diets of the pellagrous households, though apparently not an essential factor, may, nevertheless, be contributory by favoring the occurrence of a deficiency in intake of some one or more of the essential dietary factors, particularly with diets having only a narrow margin of safety. The indications afforded by this study clearly point to an increase in the availability of milk, particularly by increasing cow ownership, and of fresh meat, by all-year-round meat markets as important practical measures of prevention and control in communities of the character studied. After the manuscript had gone to press, the authors received a copy of the "Report of a Committee on Enquiry Regarding the Prevalence of Pellagra among Turkish Prisoners of War" in Egypt (published February, 1919). Among the conclusions reached, the following are of most interest in the present connection: (a) "There is no evidence of the presence of any bacterial infection standing in etiologial relation to pellagra; (b) there is no evidence of infection by any protozoal, spirochetal, or ultra-microscopic organism standing in etiologial relation to pellagra; (c) pellagra is due to a deficiency in protein as gauged by its biological value."

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**Botulism: Protective Measures and Cautions from the U. S. Bureau of Chemistry, Department of Agriculture.**—The Public Health Service (*Public Health Reports*, 1920, xxxv, 327) in an article based in part on the work of the Bureau of Chemistry, Department of Agriculture, presents the salient points in connection with the outbreaks of botulism that have been rather frequent in the United States in recent months. Ripe olives, commercially packed in glass, have been the cause of the majority of cases, though home-canned beans, asparagus and corn have accounted for some cases. Heating of food in the process of canning by immersion of the containers in hot water for a short time (one-half hour) does not suffice to kill the spores, but actual boiling of the material for such a period is sufficient. Food showing any evidence of spoilage should not be consumed.

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**Source and Significance of Streptococci in Market Milk.**—JONES (*Jour. Exper. Med.*, 1920, xxxi, 347-361) states that the principal source of streptococci in milk is the cow's udder. The udder streptococci fall into two broad groups: those of the larger group agree in cultural characters and agglutination affinities with mastitis streptococci; the smaller group is composed of low acid-producing streptococci. The streptococci of the latter group produce clear zones of hemolysis about surface and deep colonies in horse blood agar plates. They attack dextrose, lactose, saccharose, and maltose, but do not ferment raffinose, inulin, mannite, or salicin. Acid production in dextrose by the members of this group is about the same as that produced

by human streptococci under the same conditions. The limiting hydrogen ion concentration for these pleomorphic udder streptococci in dextrose serum bouillon is within the limits of the limiting hydrogen ion concentration observed by Avery and Cullen for human streptococci. All the streptococci from the vagina, saliva, skin, and feces have been non-hemolytic. Those from the saliva form a heterogeneous aggregation in which individuals fermenting raffinose, inulin, and mannite predominate. From the skin a characteristic streptococcus has been found. It produces acid in dextrose, lactose, saccharose, maltose, raffinose, mannite, and salicin, but fails to acidulate media containing inulin. The fecal streptococci are characterized by the formation of large amounts of acid in dextrose, lactose, saccharose, maltose, raffinose, inulin, and salicin. Mannite is not fermented. Neither the fecal nor the skin streptococci have been isolated from bottled milk with any great frequency.

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**Filariasis in Southern United States.**—FRANCIS (*Hygienic Laboratory Bull.* 117, Washington, D. C., 1919) made a study of the prevalence of filariasis in the large southern cities, examining the blood of several hundred persons. Charleston, South Carolina, was the only city furnishing any considerable number of infestations, and in that city 77 persons among 400 examined harbored the parasites. The few infected persons found in other cities, Columbus, S. C., Beaufort, S. C., Jacksonville, Florida, and Tampa, Florida, probably were all contaminated in Charleston, S. C., or in Cuba where this infection is widespread. The lack of spread in communities other than Charleston, S. C., is attributed to failure of parasites to multiply in the mosquito, the small number of parasites imbibed, and the necessity for a male and female embryo to find lodgment in the same lymph gland, the limited number of homes where infection is likely, the chance that the larvæ may not have penetrated the skin, and finally the chance that in the mosquito the larvæ may not reach the proboscis. While these factors are operative in both the endemic foci and elsewhere, the occasional introduction of an infected person usually will fail to start the cycle which results in the perpetuation and spread of the disease. It is said that a shipload of slaves from an African filariasis focus was landed at Charleston many years ago and the present infestation is attributed to these. Work by Francis confirmed the previously demonstrated fact that *Culex fatigans* is the host of the *Filariasis bancrofti*. The writer recommends anticulex measures to abolish the mosquito pest and to do away with the risk of infections with filariæ. Very few of the cases showed chyluria or evidences of elephantiasis.

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ORIGINAL ARTICLES.

THE MAJOR TRIGEMINAL NEURALGIAS AND THEIR SURGICAL  
TREATMENT BASED ON EXPERIENCES WITH 332  
GASSERIAN OPERATIONS.\*

*First Paper.*

THE VARIETIES OF FACIAL NEURALGIA.

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**Introductory.** The severe and incapacitating neuralgias in the distribution of the trigeminal nerve constitute an essentially neuro-surgical subject. What is more, they are likely to remain so until something which may possibly enable us to forestall the malady is learned regarding its cause and pathology.

Since Charles Bell's epochal studies a century ago on the function of the nerves of the face,<sup>1</sup> the only advances which have been made in the case of this dread disorder have been purely therapeutic, and it is safe to say solely surgical, if we may include among surgical

\* This paper and two others to be published elsewhere on the treatment of trigeminal neuralgia, formed the basis of the Nathan Lewis Hatfield Lecture before the College of Physicians of Philadelphia, December 16, 1919. At the risk of drawing this story out to an undue length, it has been illustrated by many case reports in order to give some idea of the types referred to. In most articles on the subject of neuralgia by surgeons there has been an unfortunate absence of case histories and final results.

measures the deep injections of chemicals into the nerve trunks.\* Of the disease itself we know little more than did Fothergill<sup>2</sup> in 1773, when he vividly described its symptoms, as indeed many† had done before him. He hinted that a "cancerous acrimony" might be the basis of these "stubborn evils" and recommended the extract of hemlock for their treatment. In our present century they have been ascribed to a uric acid diathesis, and such fanciful measures have been advocated as injections of rattlesnake venom—indeed, cures have been claimed from its use.

There are unquestionably many conditions loosely classified as "facial" neuralgias, though the adjective is unfortunate, for it does not refer to the seventh nerve but to the part of the body where the discomforts are located. Further confusion has resulted from the term trifacial neuralgia not uncommonly used by physicians—"trifacial" being merely an unfortunate misnomer for the fifth cerebral nerve. Thus "the face," "facial" and "trifacial," as well as other terms such as "epileptiform," variously employed in relation to the subject, have proved so misleading that the laity have clung with surprising tenacity to a French expression for the disease, which was apparently first used by Nicolas André in 1756.‡

There is unquestionably something satisfying about the words *tic douloureux* even to those who do not understand their meaning, and once heard—particularly when anglicized and with a dolorous pronunciation—they cling like a burr in the memory of all neuralgics.

"Dear Doctor: I have the tick dew la roo in the left side of my face," etc., to quote from a letter recently received from an unhappy farmer, a sufferer from the disease; and when one realizes that the designation *tic douloureux* came into common use by way of England early in the nineteenth century, the persistence of the term in remote corners of our country is the more remarkable.

The major trigeminal neuralgias have been chosen as the topic for this occasion for the reason that nearly twenty years ago—on April 20, 1900, to be exact—at a symposium on the subject arranged by this College, I ventured to describe what promised to be a less hazardous method of exposing the semilunar ganglion than those previously employed. To this we will return, for I shall hope to

\* In his memorable essay on "The Histological Relations of Medicine and Surgery" (MacMillan & Co., London, 1905), Clifford Allbutt tells of the discussion which arose in 1864 at Leeds, on the introduction of the hollow needle which Pravaz had described ten years before. Grave doubts were felt as to whether its employment for paracentesis was consistent with the traditions of purity of the physician.

† John Locke, the philosopher, among them: cf. his description of the case of the Countess of Northumberland in urgent letters asking for advice written to his friend Dr. Mapletoft (The European Magazine, 1789, xv-xvi, 185-273).

‡ I have been unable to identify this reference so often quoted. Attention was apparently first called to André's use of the term by Oliver Wendell Holmes in his Boylston Prize Dissertation on the Nature and Treatment of Neuralgia (Boston, 1838).

show how the Gasserian operation, once regarded as one of the most formidable and mutilating operations in surgery, has been so far simplified that nearly all neuro-surgeons employ practically the same operative procedure—one without ensuing deformity, and a mortality which is negligible\*.

It is a most significant thing that the victims of this dreadful affliction in its severe forms are far more frequently advised to submit to a Gasserian operation by former patients than by a profession which still regards it with misgivings. The proportion in my own series is about four to one; for typical tic douloureux in another is easily recognized by one who has himself suffered from the malady. There can be no greater tribute to an operative procedure than its recommendation to others from those who have experienced it.

A detailed description of a complicated operation makes at best a dull subject for an address, particularly before those who may not engage in surgery themselves; but the results of these measures must, nevertheless, be of general interest, and it is unfortunate that operations on the Gasserian ganglion have through their sorry past acquired a very evil repute among the profession at large. I shall hope to dispel this undeserved reputation during the course of this address, but before entering upon a discussion of trigeminal neurectomy and its results, it is important for us at the outset to know just what is implied by the term major trigeminal neuralgia and how it is distinguished from what are designated minor neuralgias as well as from other possible forms of neuralgia of the face.

Let us return for a moment to the observations of Sir Charles Bell, to which we are indebted for the knowledge that most of the "facial" neuralgias are actually due to a disorder affecting the fifth rather than the seventh pair of cerebral nerves, according to the Willisian enumeration of these structures. Until his time, the face had been thought to be a region of sufficient complexity and importance to require a double innervation, and the two nerves, *N. facialis* and *N. trigeminus*, were supposed to supplement one another, even if they did not possess a similar function. Indeed, the brother of Charles, John Bell, went so far as to advocate and practice division of the facial nerve in cases of severe neuralgia, possibly for the reason that this, of the two nerves, was the one whose trunk was surgically the more accessible. There can be no doubt but that in favorable cases some measure of alleviation may have followed a facial neurectomy, though for reasons which at the time could hardly have been appreciated—namely because of the

\* In my series of 332 Gasserian ganglion operations to December 1, 1919, there have been two deaths, the ninth and the thirty-fourth case, leaving a consecutive series of 298 operations without a fatality, with a total mortality for the entire series of 0.6 per cent.

abolition of movements which so often serve to incite the sensory paroxysms.\*

Stretching of the facial nerve, indeed, was employed well into the nineteenth century as a means of alleviating the severe cases which were accompanied by some degree of facial spasm.

Bell's differentiation of the nerves into afferent and efferent furnished an anatomical basis on which four conditions could be differentiated—those which were the result of motor paralysis and irritation, and those due to sensory paralysis and irritation. The paralytic states of insensitiveness and muscular flaccidity, which had previously appeared to have a symptomatic co-partnership, now became recognizable as separate conditions, and, on the other hand, the irritative state of *tic spasmodique* became distinguishable from that of *tic douloureux*.

We must bear in mind, however, that in these conditions motion and sensation cannot, after all, be entirely divorced. The facial nerve, for example, has its sensory radicle and the "geniculate" neuralgias, sometimes associated with an antecedent herpetic outcrop or even with a facial paralysis, may still offer some diagnostic confusion; and, what is more, the spasmodic tics in the seventh nerve distribution may sometimes elicit pain. In the case of the trigeminal nerve, on the other hand, severe neuralgic paroxysms are often associated with violent chewing movements from motor discharges involving the group of masticatory muscles.

Thus there may be a variety of painful disorders of the nerves supplying the face—disorders which are designated as "neuralgic" but which must be clearly distinguished from the more common trigeminal neuralgias with which this address primarily deals. As some of these allied conditions may be exceedingly distressing and may lead the unwary, as they have occasionally led the writer, into a needless and futile Gasserian operation, it is well to bear them in mind, so that they may be recognized if possible. Five different types may deserve consideration.

### VARIETIES OF "FACIAL" NEURALGIA.

1. The Neuralgias Accredited to the Sphenopalatine (Meckel's) Ganglion. (Sluder's Neuralgia.) In a series of papers (1908-1916) Greenfield Sluder<sup>3</sup> has called attention to the fact that the

\* It is of considerable historical interest that as late as 1828, as reported in the first number of the Boston Medical and Surgical Journal, John C. Warren divided the facial "at its root" in a case of *tic douloureux* after many unavailing operations on the peripheral branches of the fifth nerve. The operation was performed, it may be added, on the patient's insistence. A year later Charles Bell, in a paper before the Philosophical Society (read May 28, 1829, i. e., nine years after his first presentation of the subject) complained that "even now, so slow is the progress of improvement, it is stated by a surgeon that he will not hesitate to cut the portio dura in the case of *tic douloureux*."

bony partition, separating the accessory nasal sinuses from the sphenomaxillary fossa, may be extremely thin or even defective. On this basis he believes that inflammatory processes within these cells may in some cases so congest the tissues of the fossa as to produce "a symptom-complex partly neuralgic," which he attributes to involvement of the sphenopalatine ganglion. He describes the symptoms as follows:

"The neuralgic picture is pain in the root of nose and in and about the eye, in the upper jaw and teeth (sometimes lower jaw and teeth) extending backward under the zygoma to the ear, frequently making earache and pain in the mastoid; but severest often at a point 5 cm. back of the mastoid, extending thence to the occiput, neck, shoulder-blade, shoulder, breast, and when severe, to the arm, forearm, hand and fingers; with sometimes a sense of sore-throat on that side. Rarer additions to this picture are itching of the skin of the upper extremity, taste disturbances (parageusia), a sense of stiffness and muscle weakness in the upper extremity and fortification scotomata. Mild cases are described as a sense of tension in the face and stiffness or rheumatism in the shoulders. It may appear as constant pain with exacerbations, or it may stop and reappear cyclically as a migraine; or it may stop and reappear with stabbing sharpness as a tic."

Thus these neuralgias, to whatever anatomical structure they may be attributed, should be capable of differentiation from the trigeminal neuralgias, by the history or presence of sinus infection, by their frequent bilaterality, by their situation and tendency to radiate to neck and shoulder, by the more or less continuous pain which is not inaugurated by peripheral stimuli such as occurs with eating, talking, or handling the face, and by the absence of any facial contortions with the paroxysms.

Doubtless all who have seen a large number of neuralgic patients are familiar with these obscure forms of facial discomfort and it is possible that some may have been misled, as I have been, into the mistaken view that they were necessarily Gasserian in origin and could be relieved by a trigeminal resection. The following experience has made me very cautious in making the diagnosis of trigeminal neuralgia, particularly when discomforts not absolutely true to type have originated in early life.

Gasserian Series 43. October 10, 1906. *Persistent "neuralgia" of upper jaw and face unrelieved by fifth root avulsion and by subsequent removal of Meckel's ganglion.*

A woman, aged thirty-five years, a physician's daughter, giving a family history of migraine, had suffered for several years from an intractable and almost incessant pain referred chiefly to her left upper bicuspid tooth. From this point in agonizing waves it would spread over her left face, or even to her ear and shoulder. The teeth had been extracted, the alveolar arch repeatedly curetted, an



infra-orbital neurectomy had been performed, and many deep alcohol injections given at various times without any apparent relief.

Though occurring in waves of intensity the pain was not paroxysmal, nor was it incited by the usual stimuli, and the negative results of peripheral operations should have given sufficient warning of the probable futility of a Gasserian operation. The procedure was strongly urged, however, and the trigeminal root was avulsed *in toto*. There were no complications, and a total and permanent anesthesia of the trigeminal field has resulted. The pain, however, remained practically unaffected.

Dr. Sluder saw this unfortunate woman in consultation several months later, and he felt confident that it was an example of sphenopalatine neuralgia. On two occasions he attempted to inject the ganglion by his method of transnasal puncture, without securing relief. Rather than to have this process repeated, the patient, who was ready to grasp at a straw, desired that a surgical attempt be made to remove Meckel's ganglion.

This was done without difficulty through the original Gasserian approach; the base of the skull was rongeured away to the foramen rotundum; the maxillary division was followed forward and the segment of nerve crossing the sphenomaxillary fossa was removed, together with the sphenopalatine ganglion and its two connecting branches, all of these structures being easily identified (cf. Figs. 1 and 2).

Her father writes me that the area of total trigeminal anesthesia remains unaltered, but that the pain, varying in its degrees of intensity, has persisted to the present day, now thirteen years later. The patient herself writes (January 14, 1920):

"My general health is good and I look remarkably well, except when having the severe attacks of pain through my face and head, then I am very much worn and look quite pale when the pain is unusually severe.

"Since your last operation (*i. e.*, the Meckel's procedure) I have had no severe pain in the back of the head, which was always the most trying part of the pain. The initial starting and course of the neuralgia is exactly the same as I described years ago, with a trying attack every week or ten days. The constant pain is only a dull ache that I am quite used to, but when tired, which I become so easily if I do not rest for an hour or two every afternoon and retire about nine each evening, the attack starts, and then a chill air, especially if it strikes just above or behind my left ear; or a half-hour's conversation, or using my eyes in the evening, cause the pain to spread through the left side of my face and entire head, the character of the pain changing from a sore, dull muscle pain, where the tooth was pulled, to a neuralgic pain, with occasional acute nerve twists of pain, or at times a sudden sensation of knives through

the gums, or a bee sting, or as if needles were being driven through. During the past years it has become more and more painful to talk during these attacks, at times being impossible because of the pain.



FIG. 1.—Photograph, slightly enlarged, of tissues removed at operation, including Meckel's ganglion (arrow).

Several times blood has come from my left nostril after a severe attack, the sensation being the blood has come directly from the place the pain always starts, and after the bleeding the place feels like a badly bruised cut."

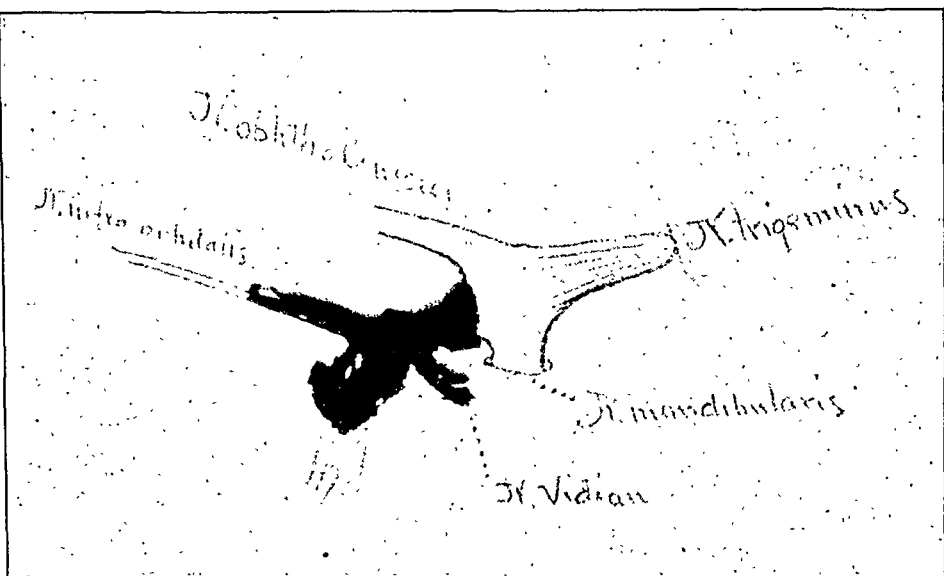


FIG. 2.—Diagram showing situation of tissues removed.

There is no explanation to offer for this experience, and the view expressed by some that there is such a thing as "central pain" capable of being referred to the trigeminal area offers no more satisfaction than does the term pseudoneuralgia or psychalgia or the adjective hysterical, which some writers use to designate these cases. However this may be, the removal of Meckel's ganglion was as unavailing as the trigeminal neurectomy, and one apparently

must look for some other source of pain in cases of this kind. They fortunately are most rare.\*

It is not improbable that Dr. Sluder's views regarding the extension of an inflammation from the adjacent cells to structures in the sphenomaxillary fossa are correct and that certain cases of neuralgia may originate in this way just as we may have a frontal or an infra-orbital neuralgia in association with frontal or maxillary sinusitis. But why an involvement of Meckel's ganglion, rather than of the adjacent maxillary nerve trunk, should be regarded under these circumstances as the probable source of pain is not entirely clear. Furthermore, from what can be read into the case reports of so-called sphenopalatine neuralgia, and they have been very meager, it would seem that the relief from pain occasionally afforded by the transnasal injection of the sphenomaxillary fossa with alcohol or carbolic acid has unquestionably been due to the spread of the fixative to the branches of the maxillary nerve in view of the resultant anesthesia in its territory, which is occasionally mentioned. Certainly, Holmes<sup>4</sup> in many instances was dealing with cases of undoubted trigeminal neuralgia.

The following is the story, briefly told, of a supposed sphenopalatine neuralgia finally relieved by a Gasserian operation. It is an example, moreover, of neuralgia of very early onset.

Gasserian Series 265. (P. B. B. H., No. 5878). *Supposed nasal neuralgia of eighteen years' duration treated by injections. Subsequent Gasserian operation, with cure.*

Admission December 10, 1916, of Miss N. J., aged thirty-four years. Since she was sixteen she has had pain in the right side of her face. At the onset it involved the region about the eye only, but soon extended to the cheek and jaws. The severest pain even now is above the eye, but the entire trigeminal area, including the tongue and the teeth, is involved in the paroxysms, during which the pain overflows to the neck, shoulder and as far as the elbow.

Soon after the onset the teeth were extracted from the right upper jaw, without avail, and for the next fifteen years her chief acquaintance was with drugs, doctors and hospitals—electricity, massage, rest cures, homeopathy, Christian Science, and, finally, when thirty-two years of age, she was taking morphin in 2-grain doses three times a day.

Two years ago she began a career of alcohol injections. (1) The mental foramen: no relief; (2) the infra-orbital, no relief; (3) a transnasal injection of Meckel's ganglion, with resulting numbness of the right palate and cheek, and relief for nearly a year. The procedure was then repeated without success, and soon afterward

\* I have met with two other examples of a very similar condition, Nos. 157 and 175 of the Gasserian series. In the former case, referred to in Dr. Sluder's volume, he attempted, without avail, to give relief which the Gasserian operation had not given, first by intranasal injections, and subsequently by a sphenoidal operation.

six successive transnasal injections were given, with some relief for about six months after the last, though she nearly died of a secondary hemorrhage from the nares.

Clinically there was no doubt but that she had typical major tic douloureux, with paroxysms produced by the usual stimuli, and a trigeminal neurectomy was performed December 16, 1916, with immediate relief and permanent withdrawal of her drugs.

December 1, 1919. Reports in person. She has gained twenty pounds in weight and has been steadily at work as a clerk. A keratitis which was untreated developed after her discharge and has left a corneal opacity. This she disregards, as she has had no pain. She has no complaints and the numbness of the face gives no annoyance.

This, then, is an example of a supposed nasal neuralgia in which a subsequent Gasserian operation cured the condition. On the other hand an example has been given of a rare form of neuralgia regarded as typical of sphenopalatine ganglion neuralgia in which pain continuing after a total trigeminal neurectomy was not subsequently relieved by injections or by the surgical removal of the sphenopalatine ganglion. In short, there is no very evident justification in the attributing of painful impulses to a disease process in Meckel's ganglion,\* and even if there were, the injection of the ganglion through the cheek would seem an infinitely less hazardous procedure. The reports of these transnasal injections with such complications as Pollock<sup>5</sup> has recently acknowledged strike one with terror and make the risks of a Gasserian operation seem child's play. But be this as it may, the experience which has been related of a futile trigeminal neurectomy shows that we must be constantly on our guard lest we mistake neuralgias not trigeminal in origin for those which are.

Whatever may be the cause of these inexplicable conditions, for they are as obscure as are the causes of migraine, an acknowledgment of debt should be made to Dr. Sluder for his insistence that there is a painful disorder of the face, the symptoms of which are unlike those of tic douloureux. At this writing there is under observation in the hospital a patient who gives the following history:

She is a young married woman, aged thirty-five years, formerly active and athletic, with no "neurotic" tendencies. Nine years ago a minute bit of steel was driven into her left cornea, causing pain and inflammation for six weeks before it was detected and removed by incision. It has left no scar or opacity. A year later she began

\* The excision of Meckel's ganglion as the supposed seat of facial neuralgia is an operation long since abandoned, though before the Gasserian ganglion operation it had a period of popularity. Unquestionably in neuralgias of the maxillary division some relief to pain was produced in view of the frequent extracranial severance of this nerve during the process of removing the ganglion. It was a difficult and bloody procedure with no physiological basis in its support. (Cf. Fowler's report of a series of cases, *Annals of Surgery*, 1886, p. 269.)

to have a sense of soreness and discomfort about the orbit. She then had an operation for gall-stones and subsequently passed through a normal pregnancy.

For eight years the periodic discomforts in the face have been progressively increasing in intensity and number. Recourse has been had to extraction of teeth, to innumerable intranasal operations and finally to drugs.

The attacks are excited without apparent cause. They begin without fortification figures, but with a feeling of discomfort about the orbit which gradually increases, with waves of agonizing, burning pain which spread over the entire left side of the face and anterior scalp, palate, jaws and teeth, and in time usually extend to the mastoid region, neck and shoulder, often reaching as far as the elbow and occasionally to the fingers. They usually reach the acme of their intensity in about an hour or two and then subside, sometimes abruptly, more often slowly, but leave invariably a feeling of soreness and stiffness of the face and mucous membranes and weakness of the arm. Recumbency makes the pain less tolerable, and she sits up tense and motionless, moaning with set expression and clenched fists, or sometimes clutching her head.

The attack having passed away, despite the resultant soreness and her anxiety lest it may recur, she feels well and ready for any activity. A sneeze almost invariably will provoke an attack, but eating, talking, handling the face never do, and there are never any paroxysmal tics. A careful physical examination, with roentgen-ray studies is quite negative. The only positive finding is a Wassermann reaction in the blood. The cerebrospinal fluid is negative.\*

I am at a loss to know what to call this condition, though it certainly is not a trigeminal neuralgia. It is unquestionably the disorder that Dr. Sluder is describing, and whether or not it is to be attributed to Meckel's ganglion or to some disorder of the sympathetic system we may with all justice refer to it by the name of Sluder's neuralgia even though its origin in the sphenopalatine ganglion is extremely doubtful.

I have seen six to eight of these cases, and the experiences I have detailed have led me to beware of them. Owing to their resistance to the usual surgical measures which give relief to the trigeminal neuralgias it is important that they should be recognized, and it

\* This patient was under observation for a long period and endured a most vigorous antiluetic regime, without affecting her pain in the slightest. Deep alcohol injections were then employed, first into the maxillary division, the palatine branches being the first affected in the resulting numbness, so that Meckel's ganglion was almost certainly thrown out. An extensive herpes of the hard palate followed but no apparent relief of pain. Later the supraorbital nerves were divided and still later the mandibular nerve was injected. Her paroxysms remain largely unrelieved.

The question might be raised in this case of a possible tabetic neuralgia, but if such a thing exists it must be extremely uncommon and only when other signs of tabes are manifest would such a diagnosis be justifiable.

is in cases of this kind that trial injections of alcohol into the main nerve trunks may be of diagnostic value. The conditions, however, cannot be very common. Certainly they are less common than Holmes's article would lead us to believe, and an overflow of pain to the neck, shoulder and even the arm is by no means uncommon in the true tic douloureux cases.

The clinical histories of the 332 patients in this series show that next to the extraction of teeth, nasal operations are by far the most frequent of minor surgical measures to which these unfortunates have been subjected. Usually there has been no relief and rarely has any actual nasal trouble been disclosed, though in bad cases the mucous membranes as well as the skin doubtless suffers from neglect and from nutritional disturbances. In a few instances, however, an actual chronic infection may be present and yet the Gasserian procedure be clearly indicated. The following is an example of a fairly long-standing neuralgia in a comparatively young woman, associated with a definite nasal infection

Gasserian Series 276. (P. B. B. H., No. 6534). *Major neuralgia, with onset at twenty-seven and of nine years' duration, in a young woman with chronic nasal diseases.*

April 2, 1917. Admission of Mrs. M. T., aged thirty-six years.

In 1908 pain began in the left third division at a point slightly anterior to the tragus. After a few months it extended down into the lower lip and began to radiate upward into the auriculotemporal distribution.

In 1910 the second division became involved, first in the upper lip and roof of the mouth; a few months later in the nose and the lower lid.

Since 1914 the first division has been involved in the paroxysms by extension of the pain up through the eye and over the forehead to the vertex.

From 1912 to 1915 the attacks became gradually more severe, with practically no cessation, though occasionally there would be a day or two of freedom. Eating became impossible and for weeks at a time she subsisted on liquids. Her face would become badly flushed and there was marked lacrimation during an attack. She got some relief during the paroxysms by firm pressure along the left side of the nose and below the left zygoma.

Her worst period was three years ago, during a pregnancy, and she is said by her local physician to have attempted suicide twice. During 1915 the attacks were somewhat less severe, with freedom of two to three weeks at a time. She attributes this to the fact that she had given up all attempts to do her housework. At present she has four or five attacks a day lasting three or four minutes. Coughing or eating always starts an attack, as does washing the face or brushing the teeth. As pressure on the teeth caused tic the second and third lower molars were removed but found normal. Many

alcohol injections have been given without relief. Beginning in 1914 innumerable nasal operations were performed. First the tonsils were excised. Then a "broken bone" was removed and pus found in the left antrum. In 1915 the antrum was tapped without result and the turbinate bone "trimmed." In 1916 the antrum was again tapped and some polypi removed. The anterior ethmoid cells were also opened and said to be infected. She does not attribute her moderate relief, which began in 1915, to these operations, though it was coincidental.

April 6, 1917. The sensory root was avulsed, leaving a total trigeminal anesthesia. She made a perfect recovery.

October 20, 1919. *By letter.* "There is no need of telling you I have no pain in my face, though at times I feel the bad effects of getting too tired. My face feels then as if made of metal and very heavy, but no one would ever know there was anything the matter; in fact there is not, with that side of my face, and my eyes are better than ever.

"The summer following my operation I worked harder than ever before in my life. As my boy had been drafted, I hired out to my husband and did a man's work in the field, ploughing, harrowing, cultivating, hoeing, weeding; ran a mowing machine, hayrake, cradled rye and bound it. I worked from sunup till sundown; got terribly tired and tanned, but finished the fall work in A-1 health.

"In addition to farm work I sold \$35,000 Liberty Bonds among the farmers . . . so you can see I was busy with trying, nervous work, feeling no bad results whatever, sleeping and eating at regular times and doing both heartily. . . I am in A-1 shape, although the nasal trouble is still bad, due to the 'terminated bone' in my nose, if that's what you call it. I have written this to show you I have been actively doing nerve-racking work and have had no bad results, though I was once told I could do nothing. . . .

"I had occasion to call on Dr. C——, to tell him what I had been through during the last ten years. I wish you could have seen his face as he tested the nerve. Twice he has sent for me to meet other physicians who are as incredulous as he. All are very much amazed at the seeming lack of facial paralysis".\*

Thus examples have been given of some forms of neuralgia which might possibly be attributed to the sphenopalatine ganglion. In one of them, though regarded as a typical case, neither the Gasserian nor a subsequent sphenopalatine extirpation relieved the trouble. In another, regarded also as a sphenopalatine case, the Gasserian operation was curative, and in the third, obviously a case of extensive nasal infection, the same operation was equally successful. Nevertheless there exists a clinical type of facial neuralgia which

\* This last paragraph is of interest as an evidence of the prevailing belief that a Gasserian operation leads to a marked deformity.

does not conform to the classical descriptions of *tic douloureux* and may deserve to be designated as Sluder's type of neuralgia, whether or not his anatomical explanation of its origin will come to be accepted.

2. **The Post-Zoster Neuralgias (Trigeminal and Geniculate).** It is generally believed that even the minor forms of facial herpes, nasal and labial, are due to some mild infective process involving the Gasserian ganglion. However, even when facial herpes is fairly extensive, as it may be in severe cases of pneumonia, meningitis, typhoid or other febrile states, it is not supposed to leave any subsequent discomfort in the involved area.

But it is otherwise with true zoster, particularly when extensive skin lesions occur in the middle-aged or elderly, for then so-called post-zoster discomforts of a neuralgic kind are apt to supervene. At times they may be most distressing and completely incapacitating. This is no less true when the trigeminal skin field has been the seat of the herpetic outcrop than when other zones of the body have been involved.

When zoster occurs in the trigeminal skin fields and the lesion is followed by neuralgia the discomforts do not, as a rule, tend to spread into the territory of the other divisions, and in this respect these neuralgias differ from the true *tic douloureux*. The pain, moreover, is described as having a persistent burning character, and thus does not resemble the sharp and paroxysmal attacks of true trigeminal neuralgia. Ordinarily the condition is easily recognized by the history and by the cutaneous scars of the original lesion.

The three examples of zoster neuralgia of trigeminal origin which I have seen followed in each case a severe involvement of the ophthalmic division. In only one of them (Gass. Ser. 325) has a trigeminal neurectomy been performed. In both the others the supra-orbital nerve was avulsed, with no great permanence of relief, but in neither were the discomforts sufficiently severe to call for an intracranial procedure.

The relation of mild meningeal infections to trigeminal herpes in its various forms, through Gasserian involvement, and the possible relation of these lesions to subsequent neuralgia, need not be gone into here, for I do not know that I have anything essential to add to a former report on the subject.<sup>6</sup> The following case history, however, of a patient in whom facial neuralgia followed an attack of cervical zoster severe enough to leave scars may be pertinent to this discussion of varied forms of neuralgia. The case is a confusing one, being an example of bilateral neuralgia involving only the two lower trigeminal divisions. It was regarded at the time as a possible example of sphenopalatine involvement, though there was no history or clinical evidence whatsoever of any sinus trouble.

Gasserian Series 58. *Bilateral facial neuralgia of fourteen years' duration, following cervical zoster. Many operations, including a*



*trigeminal root avulsion on the left and an intracranial resection of the maxillary division, together with Meckel's ganglion on the right.*

July 9, 1907. Admission of Mrs. J. B., aged fifty-six years. In 1895 she suffered from a severe meningitis with pneumonia. During the illness there was an extensive nasolabial herpes, and while convalescent an outcrop of zoster occurred in the cutaneous distribution of the left fourth cervical segment. Characteristic zoster scars persist on the side of the neck and over the angle of the jaw.

Subsequent to this illness she began having stinging pains not only in the left neck but on both sides of the face. The discomforts originated in 1895 in the left maxillary division, and in 1899 extended to the mandibular division. Though the pain was more or less continuous, paroxysms occurred simulating typical *tic douloureux*.

In 1900 pain appeared in the right infra-orbital region and soon involved the right mandibular area. This right-sided neuralgia became so severe as to dominate the condition and was described as a continuous pain, with severe paroxysms. Complete physical incapacitation resulted therefrom.

She first came under observation in 1902, after seven years of neuralgia. At that time both infra-orbital nerves and the right inferior dental nerve were peripherally avulsed. She had complete relief for two and one-half years.

In 1905 she was readmitted, owing to a return of pain, chiefly referred to the left mandibular division, where no operation had as yet been performed. Encouraged by the former operations the left inferior dental was then avulsed by trephining the angle of the jaw. She had considerable relief for twelve months.

In 1907 she was again admitted, owing to a return of severe pain in the left face, the second and third divisions only being involved. By this time sensation had largely returned in the anesthetic areas. She was suffering so greatly that a Gasserian operation was performed; the left sensory root was avulsed, with resultant total three-divisional anesthesia and paralysis of the masticatory muscles. From that time to the present she has had no pain in this territory.

In 1908 severe discomforts returned in the right face. Numerous deep alcohol injections were made in the nerve trunk and the infra-orbital operation was again repeated. There was some amelioration of the pain for a few months.

In 1909 she reappeared, owing to a return of the right-sided pain. A double trigeminal neurectomy, in view of the motor-fifth paralysis of the right, was out of the question.

The possibility of sphenopalatine neuralgias were under consideration at this time, and after consultation with Dr. Sluder the right Gasserian ganglion was exposed and the maxillary division, together with the contents of the sphenopalatine fossa, including Meckel's ganglion, was removed. This led to a total anesthesia of the mucocutaneous field supplied by the second division, as shown in Fig. 3.

in addition to the left total trigeminal anesthesia (Fig. 4), due to the neurectomy of 1907.

In 1919 she writes that she had a period of relief for two years, but has been obliged since then to take recourse to deep alcohol injections, which give periodic relief in case the regenerated right maxillary nerve happens to be infiltrated.



FIG. 3



FIG. 4

FIGS. 3 and 4, Case No. 58.—Showing areas of anesthesia, total left, second division right, after final operation.

This, then, was an example of bilateral neuralgia following herpes zoster, with no apparent infection of the sinuses, but with an involvement on both sides of only the second and third divisions, suggestive of the type of case which Dr. Sluder has described. However, the trigeminal root was avulsed on the left side twelve years ago, with subsequent freedom from pain in this area. On the right side Meckel's ganglion, together with the maxillary division, was removed ten years ago, with relief for only two years—in short, a period of relief only about as long as would be expected in the case of division of the maxillary nerve itself. The removal of Meckel's ganglion on this side has not appeared to affect the condition in the slightest.\*

\* In only one other case in the entire series of 332 was a definite bilateral neuralgia present at the time of the Gasserian operation. In both cases the greater severity of the symptoms on one side demanded relief by a trigeminal procedure. A questionnaire reveals that several other patients in the series have been made apprehensive by twinges of pain on the opposite side of the face, coming on at varying periods subsequent to the neurectomy.

It is possible that I may be laying too much stress upon these rare conditions, but it is desirable that they be as clearly portrayed as possible before we come to consider the subject of the uncomplicated unilateral major neuralgias.

3. The Neuralgias Accredited to the Geniculate Ganglion (Neuralgia Facialis Vera: Hunt's Neuralgia). Particular attention has been paid by Ramsay Hunt in an important series of papers (1907-1915<sup>7 8 9 10 11</sup> to the clinical importance of the sensory radicle of the facial nerve exclusive of its gustatory function. He has emphasized the fact that discomforts may occur in the auricular skin field, which he attributes to the geniculate ganglion, a structure which is, of course, the homologue of the semilunar ganglion, and he even speaks of "a primary tic douloureux" of the ear among other forms of otalgia. It is quite possible, therefore, that some of these conditions may lead to diagnostic errors and be confused with trigeminal neuralgia, and it gives an additional reason for refraining from the use of the term facial neuralgia as a general designation for the various forms of pain in the face.

Hunt has collected many examples<sup>8</sup> of auricular herpetic inflammations, unquestionably geniculate in origin, some of which have been followed by discomforts similar to the discomforts succeeding zoster elsewhere. It is possible that these conditions may be more common than is generally realized, though since interest was aroused in the subject through Hunt's interesting studies no examples of neuralgia which could with justice be attributed to the sensory division of the seventh nerve have been admitted to the Brigham Hospital clinic.

The otalgias<sup>11</sup> which result from geniculate disease are said to be at times very severe, and, what is important in our present connection, the discomforts may actually spread forward over the trigeminal field and down the neck and shoulder, so that they may easily be confused with other pseudotrigeminal neuralgias.

One very extraordinary case of "tic douloureux of the sensory system of the facial nerve" has been briefly reported by Clark and Taylor.<sup>12 13</sup> An intracranial operation was performed with division of the facial, the pars intermedia and the upper fasciculus of the acoustic nerve. The patient was said to have made a complete recovery.

The subject is a most interesting one and has been presented most convincingly by its chief sponsor; but it would seem, in view of the situation of the geniculate ganglion and its necessarily frequent implication in infections of the middle ear, that otalgias from this source would certainly be as frequent if not more frequent than similar conditions in the field of the trigeminus. Certainly the two conditions must be different in their nature, and to avoid confusion it would seem unwise to speak of the geniculate syndrome and its otalgias as *tic douloureux*:

It must be borne in mind, furthermore, in the consideration of otalgias, that the trigeminal skin field has been shown<sup>14</sup> to include the tragus, the anterior wall of the auditory canal and part of the tympanic membrane, and in many cases of trigeminal neuralgia originating in the mandibular division the inaugural pain in the auriculotemporal neighborhood is often described as starting in or near the articular process of the jaw.

4. **Painful Tic Convulsif.** This, so far as I know, is an undescribed condition. I have seen three definite cases. One of them I operated upon myself, another was operated upon during my absence overseas by one of my colleagues and the third I refused to operate upon. As already indicated the spasmodic contracture of the face which characterizes motor tic may in aggravated cases be accompanied by great pain. Occasionally examples of this condition are seen which so far resemble Gasserian cases that one unfamiliar with the disorder might be led to believe that the condition was actually trigeminal in origin. The deception is the more likely to occur because of the facial contortions and masticatory movements on the involved side which sometimes accompany the paroxysms of true trigeminal neuralgia. It is improbable, however, that the two conditions would be often confused even were painful spasmodic tic a more common malady.

The following history tells of an outstanding failure in my early experience with Gasserian operations:

Gasserian Series 93. *Unilateral painful facial spasms of many years' duration. Various operations, including Gasserectomy unavailing. Spinofacial anastomosis after peripheral division of seventh nerve.*

Col. J. L., aged fifty-two years, entered the Johns Hopkins Hospital in May, 1909, with a history of twelve years of severe neuralgia. It originated in the ophthalmic division in 1897, extended to the maxillary division in 1899 and soon after involved the entire trigeminal field. From the outset the condition had been characterized by marked motor spasms, which, indeed, seemed to inaugurate the paroxysms (Fig. 5).

Owing to the original pain being referred to the eyeball, a surgeon had removed the eye in 1897. The following year a supra-orbital neurectomy was performed. In 1904 all the teeth were extracted. In 1905 an ineffectual attempt had been made by the Hartley-Krause method to remove the ganglion, and two years later another desperate and ineffectual attempt had been made. The intervals between these operations had been occupied in an unavailing search for relief by drugs, electricity and change of climate. Nothing had given relief; he was in desperation and suicidal. The lower right face was the seat of a distressing hypesthesia dolorosa, and he compared the sensation of his facial spasms to that of a red hot skewer being thrust through his face and twisted up.

On June 18, 1909, the remains of the ganglion and its sensory root

were removed, leaving for the first time a total anesthesia of the trigeminal area. The spasms and pain continued unabated.



FIG. 5, Case No. 93.—Patient on admission, showing character of facial spasm.

On July 12 the right facial nerve was exposed in the Fallopian canal and an effort made to destroy the geniculate ganglion. A spinofacial anastomosis was then made. This was followed by disappearance of the tic and the first moderate relief he had had for years, though it was not complete, for he still complained of pain in his jaw.

After a six months' interval the spasms returned over the spino-facial route. The pain gradually increased, extended into his ear and became so insufferable that some further aural operations were undertaken at his home, after one of which, on October 28, 1913, death brought the only real relief he had had in sixteen years. A postmortem examination, according to the report, demonstrated the totality of removal of the right trigeminus, but the examination was otherwise negative.

Another case of exactly this same sort was operated upon by the hospital resident during my absence abroad. The pain began in the eye, and six months later there followed a blepharospasm which gradually increased until it involved the lower parts of the face as well. The pain likewise had spread into all three divisions and there had been marked complaint of pain back of the ear and her sufferings were intolerable. The ganglion operation was successful and total, and there was some possible relief for two or three months. Since

then the facial spasms have been returning with as much pain as before, though the area of anesthesia remains complete over the entire trigeminal territory.



FIG. 6.—Painful tic spasmodique.



FIG. 7.—Further example of painful facial spasm.

We are brought back, in cases of this kind, as in the first one here reported, to the question which some have raised of the possibility of pain of central origin. All that one can say in our present connection is that these were not examples of true trigeminal neuralgia. Fortunately experiences of this sort are excessively rare.\* However, there can be little doubt but that the undeserved ill-repute of the surgery of the Gasserian ganglion has been due to three factors—to fatalities through surgical inexperience, to incomplete neurectomies which have permitted nerve regeneration and lastly to occasional unsuccessful trigeminal operations on patients with pain not trigeminal in origin, though seemingly referred to its areas of distribution.

\* I have seen another very similar case of major convulsive tic, with pain, in which a Philadelphian surgeon had likewise performed a Gasserian operation without relief (Fig. 6). The patient subsequently died and an autopsy revealed no apparent cause of the disorder. In still another case in which pain accompanied the motor spasms a spinofacial anastomosis permanently cured the condition. These conditions may possibly be attributable to a lesion of the geniculate ganglion, as suggested by Hunt.<sup>9</sup>

5. Neuralgias from Tumor Involvement. Though comparatively uncommon conditions\* these may be due to tumors arising in various places. They may be divided into four groups: (1) The *tumors in the cerebellopontile recess* which press upon the trigeminal root; (2) *those involving the ganglion by direct pressure from above*; (3) *those arising in the pterygoid fossa or in the temporal bone*, which press against the ganglion from below; and (4) *those arising from the envelopes of the ganglion itself*.

(1) In the acoustic tumors, which are typical of the first group, the neuralgia, to judge from my experience with some forty surgically verified cases, is an inconspicuous and fluctuating feature of the condition and is rarely severe. Nevertheless, cerebellopontile tumors appear to be capable of producing paroxysms which resemble *tic douloureux*, and oft-quoted examples have been cited by Krause, by Lexer and by Weisenburg. In all of these, futile ganglion operations had been performed. The tumor in Krause's case<sup>16</sup> was a cholesteatoma of the angle, in Lexer's case<sup>17</sup> a psammoma and in Weisenburg's case<sup>18</sup> an undoubted acoustic neuroma, which certainly at the present day would have offered no difficulty in diagnosis to one familiar with the symptomatology of these lesions. It would appear, therefore, that, though tumors in the cerebellopontile angle are capable of producing severe neuralgia, it is a rare symptom of the acoustic neuromas, by far the most common of the angle tumors.

(2) The tumors of the second group, which arise in the middle fossa, press upon the ganglion from above and thus produce trigeminal discomforts, are liable to be growths with a meningeal attachment—the endothelial tumors, granulomas and occasional gliomas. As a matter of fact, however, in my experience the neuralgias from lesions of this sort are inconspicuous, and though they may occasionally be of some localizing value, they are so overshadowed by the general pressure disturbances as to be a minor symptom of the underlying disorder. They certainly would never lead to a ganglion operation on the assumption that the neuralgia was the primary trouble. Most of the cases of this type in my series have been meningeal endotheliomas which arise with a broad base from the sphenoidal ridge, and in the course of time so fill the middle cerebral fossa as to press on the dura overlying the ganglion. They are easily distinguishable from the endotheliomas which arise directly from the ganglionic envelopes.

\* I find in my series of 550 intracranial tumors in which the histological nature of the lesion has been verified by operation or autopsy that there have been eight cases (four of them endotheliomas) in which an involvement of the trigeminus has been the outstanding feature of the case. Five of these cases were subjected to a palliative trigeminal neurectomy, with no fatalities. Hellsten,<sup>15</sup> in 1914, collected 23 cases in the literature and doubtless a careful search would reveal many more under various titles.

It is astonishing to what an extent the ganglion may be flattened and distorted by extreme degrees of intracranial pressure without the production of any discomforts. Fig. 8 shows in its natural size the ganglion removed postmortem from a patient who had an enormous endothelioma of the hemisphere at a distance. Both Gasserian ganglia were flattened to paper thinness, and cerebral herniations, fragments of which can be seen in the photograph attached to the second and third divisions, had actually crowded their way far into the foramina of exit of these nerves. There had never been any complaint of discomforts.



FIG. 8.—Gasserian ganglion (natural size), showing flattening from pressure due to cerebral endothelioma, also cerebral herniations broken off with the second and third divisions.

(3) Tumors which arise in the cranium or the extracranial tissues beneath the ganglion, often metastatic, are almost certain to involve the structure in the course of time. Occasionally the nerve may be completely destroyed by the invading growth, leaving a total anesthesia in its territory without the production of pain, and several examples of this occur in my tumor series. More often the process is accompanied by a grinding neuralgia which may possess paroxysmal characteristics sufficiently severe to demand an attempted neurectomy as a palliative measure. There are four cases of this type in my tumor series: an osteochondroma of the petrous bone, an epithelioma of the middle ear, a metastatic carcinoma from the breast and an adamantinoma of the jaw. The last of them may be given as an example.

Gasserian Series 318. *Recurrent adamantinoma of the lower jaw invading the middle cranial fossa, with severe neuralgia.*

September 5, 1919. A physician, aged forty-six years, had had the left mandible resected in 1902, owing to a tumor growth which proved to be an adamantinoma. Twelve years later, in 1914, owing to a recurrence, an extensive resection was made of the tissues in the pterygoid fossa.



Three years after this procedure he began to suffer from severe grinding continuous pain in the first and second trigeminal areas. There was no sign of local recurrence and an operation was discouraged, owing to the belief that the pain was due to the nerves being caught in the extensive extracranial scar. The pain did not subside, and two months later the middle cerebral fossa was explored. A nodule of the tumor was found protruding through the base of the fossa, a much distorted ganglion being found crowded to its inner side. On removal of the tumor mass it was possible to locate the sensory root which was avulsed *in toto*, a complete anesthesia of the trigeminal field resulting. His pain was completely relieved.

(4) The endothelial tumors which arise from the envelopes of the ganglion itself constitute in our present connection a far more interesting and important group of cases, for so far as I am aware they inevitably give severe pain. Though in the past these lesions may have been difficult to diagnose, so much so that the tumors have usually been an accidental surgical finding in the course of a Gasserian operation, this could hardly happen at the present day. It is inevitable that a relative hypesthesia, if not an actual sensory and motor paralysis, should accompany the process and clearly distinguish it from an essential neuralgia even if the character of the pain did not arouse suspicion.

At the time of the symposium I have mentioned, Dercum, Keen and Spiller<sup>19</sup> reported *in extenso* a case of endothelioma of the ganglion, then regarded, as it still may be, as a condition of some rarity. The diagnosis had been previously verified by the removal of an involved cervical gland, but the neuralgia was so intense that two successive attempts were made by the Hartley-Krause method to expose and remove the Gasserian ganglion together with the tumor.

In view of our fundamental conceptions of the function of the fifth nerve the extraordinary part of their report lay in the explanation offered for the persistence of sensation in the trigeminal skin fields after the operation, for the ganglion was supposed to have been excised in its totality. One can possibly understand persistence of pain after the removal of the ganglion as in the cases already cited, but it is very difficult to account for persistence of sensation on any other basis than an incomplete extirpation. Charles Bell would rest uneasy in the churchyard at Hallow-on-the-Severn if he thought that anyone would come to believe that the facial nerve could take the place of the trigeminal by a gradual substitution of function, or could explain, as has been done, the occasional facial palsy which follows a Gasserian operation on the basis of a motor supply to the expressional muscles by way of the fifth nerve.

These trigeminal endotheliomas are most interesting tumors, and arise, as do the meningeal endotheliomas elsewhere, from the arachnoid villi, which project into the dura. Unlike the usual menin-

geal endotheliomas, however, many of these trigeminal growths remain for a long time largely extradural, and though they may in time penetrate the overlying membrane and invade the middle fossa, their tendency is to erode the cranial base and also to crowd their way backward through the dural foramen alongside the fifth root and expand in the posterior fossa, where they may reach a large size and simulate a primary cerebellopontine lesion.

Hellsten,<sup>15</sup> in 1914, not only reported a case of his own, but in a review of the literature of the subject refers to twenty-three additional tumors of the ganglion, six of which were diagnosed as endotheliomas, and many of the nine so-called sarcomas and fibrosarcomas, including his own case, were probably of the same nature. Frazier<sup>20</sup> has recently recorded the most successful case in the literature, one which shows the importance of early exploration. He has collected reports of 43 cases, more than half of them endotheliomas or sarcomas. Doubtless a search would reveal many more examples hidden in medical papers under various titles, though, as Frazier has pointed out, comparatively few of them have been disclosed at operation—namely, 13 out of the 43 cases of which he found record.

There have been four typical cases in my series, the more recent of which may deserve a brief report in view of the fact that our first impression led us to suspect an acoustic neuroma.

Gasserian Series, 328. (P. B. B. H., No. 11457). *Endothelioma of the left Gasserian sheath producing severe neuralgia, with increasing anesthesia.*

November 7, 1919. Admission of Mrs. S. E. K., aged forty-two years, always a nervous woman, a victim of "sick headaches." She received a blow seven years ago on the left side of the head which was not regarded as serious. Her present trouble began eighteen months before admission, with tinnitus in the left ear, followed by gradual loss of hearing and some dizziness and unsteadiness. For a year there has been complete deafness. For six months there has been pain, largely in the ophthalmic division, and for one month numbness of this part of the face with palsy of the left oculomotor nerve. Her discomforts were extreme and were typical of increasing pressure of a tumor against the fifth nerve.

Examination showed an involvement of the left third, sixth, fifth and eighth nerves. There was a complete motor-fifth paralysis, almost complete loss of sensation in the brow and partial loss in the maxillary skin field. The roentgen ray showed an extensive erosion of the sella turcica.

There was a median tumor of the thyroid which was hard, and it was thought possible that there might be a cranial metastasis, though the diagnosis of endothelioma was favored.

A two-stage osteoplastic operation in the temporal region was performed. At the first stage the growth was identified as an

endothelioma, and it was separated from the skull well down to the region of the ganglion. At the second session the dura was opened, and though it was found that the tumor had broken through so that a mass the size of a walnut projected under the temporal lobe, the larger part of the growth lay between the dura and the skull enclosing the ganglion. The ganglion, though largely destroyed by and incorporated within the tumor, nevertheless was identified and traced back to the sensory root, which was avulsed. The tumor had pushed its way through the dural opening for the sensory root and extended into the posterior fossa, accounting for the involvement of the acoustic nerve. The operation necessarily was an incomplete one so far as tumor extirpation was concerned, but the avulsion of the sensory root, with resultant total anesthesia, has served to alleviate her discomforts.

The description of the postmortem findings in Homen's<sup>21</sup> case corresponds closely to those described above, for the tumor had similarly found its way through the dural foramen for the sensory root and projected into the posterior fossa, and in Hellsten's case the subtentorial tumor expansion had led to symptoms pointing particularly to the hind brain.

I have possibly gone into these tumor neuralgias in too great detail, for they are not common and should be easily recognized. I desire, however, to warn those who may come to undertake Gasserian operations of the mistakes in diagnosis that may be made. To one of them I attribute the first of the two fatalities in my series. This was seventeen years ago and the ninth case in the series, and from what can be read into the history at present I assume that the patient had an unrecognized acoustic tumor. He was totally deaf and was blind, whether from a primary or secondary optic atrophy is not clear. He was bedridden, so that no note was made regarding his gait and station, and his constant complaint was of an intolerable pain in the left face. These were days before I had much understanding of brain tumors in general, far less of cerebellopontine tumors in particular, and with the assurance of youth based upon an experience with eight successful cases, a Gasserian operation was undertaken. This disclosed a separation of the sutures and a very tense dura, and there was a respiratory failure before the ganglion could be exposed. Unfortunately no autopsy was permitted, and I have felt obliged to include the case as a fatality in the series.

**6. The Minor Trigeminal Neuralgias.** These are multitudinous. They may follow injuries, particularly when nerves have been contused or more seriously damaged. They are particularly common as the aftermath of dental procedures and the prevalent root infections are a frequent source of neuralgic discomforts. Again, the extension of nasal infections to the accessory sinuses, frontal, sphenoidal or maxillary, is a common precursor of neuralgia, due unquestionably to some inflammatory involvement of the adjacent nerve trunks.

Most of these conditions are too well known to deserve special comment: their form of treatment is more or less obvious. Occasionally, it is true, neuralgic discomforts in the distribution of peripheral branches of the trigeminus may persist and may demand something more than measures directed to the inciting cause, an alcohol injection into the nerve trunk or even a peripheral neurectomy.

Oftentimes, it must be confessed, conditions which we have placed in the category of minor neuralgias are regarded by the patients themselves as most intolerable, but we have done so for the reason that only a single division has been involved, and on due consideration it has seemed unwise to perform a Gasserian operation even when intense pain is complained of. An example may be given.

Surgical No. 10796. Miss N. M. C., an unmarried woman, aged fifty-six years; never particularly robust and now profoundly neurotic, entered the hospital July 10, 1919, with a history of having struck her right eye against the corner of a gate six years previously. The eye became very painful and six months later it was enucleated. The wound became infected and there was a continuous discharge for two years, severe supra-orbital pain having been continuous during this period.

In 1915 the orbital contents, including the conjunctiva and lid margins, were removed and the skin closed over the fossa. For a year there was relief, but the pain returned and has been persistent ever since. It is limited to the brow. It is more or less continuous, and there are paroxysms incited by slight stimuli. Alcohol injections eight in all, have been given, with more aggravation than relief, and she has taken large doses of morphin.

On July 12, 1919, a supra-orbital neurectomy was performed, with a resultant anesthesia of the brow and lids. There has been practically no alleviation of her discomforts.

It is difficult to know in a case of this kind whether a Gasserian operation is indicated. The patient is completely incapacitated, but in view of her general characteristics I have little doubt but that she would continue to complain of discomforts even after a trigeminal neurectomy. This is the type of case from which the major operation has been withheld. It doubtless represents the type of single division neuralgia which offers difficulties to all in coming to a decision as to the proper form of treatment.

When some definite irritative lesion is found, one may look with more or less equanimity on these local neuralgias, but in the cases in which the initial paroxysm, unrelated to any discoverable cause, strikes unannounced and others tend to follow, one must realize that these attacks may be the precursors of the major type of neuralgia.

It is a matter of importance that this be recognized, if possible, if for no other reason than to spare these unfortunates from the usual sequence of minor therapeutic procedures, which begin with the

extraction of unoffending teeth until all of them may be drawn, with intranasal operations, until all the sinuses have been explored, with peripheral neurectomies often repeated, with electric treatments, violet rays, osteopathy and drugs without end, until purse and patience are exhausted and a physical and financial wreck results.

Few maladies can vie with trigeminal neuralgia for the number of therapeutic measures which have been earnestly advocated. The long and short of it is that in the early stages of the disease both patient and physician may be deceived, for if any medicinal measure is persisted in long enough, particularly if the patient is kept quiet meanwhile, a cure will appear to have been effected, for the malady is characterized by remissions from pain which may be as abrupt as their onset, and if the remission happens to coincide with the taking of a new drug or novel therapeutic measure, it will be given the credit. Thus doctors are likely to gain erroneous impressions of the therapeutic value of a given measure, for the patient on the return of pain is prone to seek a new physician with a new remedy.

Recourse to morphin should be had only as a last resort. Some of the worst possible cases of morphinism may be acquired in these conditions,\* but, so far as is known, all of the patients in this series except one, a physician, I regret to say, have been broken of their habit during convalescence from their ganglion operation. Morphin in sufficiently large doses to alleviate the paroxysms when they occur would suffice to profoundly narcotize the patient in the interval, and the pain is so dreaded that they are liable to continue with the drug when it is once started, in the hope of warding off attacks.

There are, therefore, minor stages of true major neuralgia, as might be expected, for the disease steadily progresses in its severity and in the extent of involvement of the areas supplied by the three divisions of the nerve.

From a surgical point of view it is desirable to indicate, so far as possible, the standard whereby one comes to regard a case of true trigeminal neuralgia as of major type and another of minor type, for only in the case of the former would one feel inclined to suggest so radical a procedure as a Gasserian operation, for in spite of its effectiveness in stopping pain it has certain drawbacks, as I shall point out.

These early cases, with the periods of freedom lasting for months at a time and with the pain largely confined to a single division of the nerve, are the ones which we have come to designate minor neuralgias—sometimes to the indignation of the victims thereof it may be admitted, for excruciating pain may be confined to a single division. However, we have drawn this distinction as a measure of severity, extent and duration of the disease, the minor cases being

\* Patrick does not regard them as common but the cases in this Gasserian series represent a far more advanced stage of the disease than that he has described.

those in which some temporary measure like a peripheral neurectomy or alcohol injection has been resorted to, and the major ones, those in which it was only too obvious that prompt recourse must be had to a Gasserian operation.

I have not kept so careful a record of the minor cases as of the others, for many of them have not entered the hospital but have received injections as out-patients. In the Brigham Hospital records there have been 195 cases recorded as major neuralgia in which the trigeminal root has been avulsed, and only about 50 cases indexed as minor neuralgia, many of them patients with frequent readmissions, and a considerable percentage of them cases in which subsequently a Gasserian operation was called for.

Although in a number of instances in the series patients with a major type of neuralgia involving all three divisions have been subjected to a primary ganglion operation, one is nevertheless averse in the long run to taking this radical step without some preliminary measure, and it is here that alcohol injections, except in the case of supra-orbital neuralgias, serve the purpose far better than the old-time peripheral neurectomies. This procedure has come into such prominence of late, and has such definite possibilities as well as limitations, that it deserves discussion in a special section of this address. It is a measure which should be limited to the minor neuralgias or as a means of aiding in the diagnosis of such major cases as may have an obscure symptomatology suggesting some form of pseudoneuralgias such as has been described above.

**Summary.** Five types of facial neuralgia capable of being mistaken for trigeminal neuralgia have been described; those ascribed to the sphenopalatine ganglion, those secondary to zoster, those attributed to the geniculate ganglion, those accompanying certain cases of convulsive tic, and, lastly, those due to an involvement of the trigeminus by tumors. Finally, an attempt has been made to describe what are considered minor trigeminal neuralgias as distinguished from major trigeminal neuralgias, for which the Gasserian operation is unquestionably the proper therapeutic procedure. It is, of course, merely a question of degree, but it is important to have some basis for separating them.

In the case of the five types of pseudotrigeminal neuralgia which may be mistaken for trigeminal neuralgia there is every reason to refrain, if possible, from a trigeminal neurectomy.

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## NUMBER OF RADIOGRAMS AND ROENTGEN-RAY BURNS.

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THE maximum number of exposures in a given case that can be made without producing a roentgen-ray burn, an erythema or a temporary or permanent alopecia can be obtained by the formula used for determining unfiltered dosage. The principle of this formula is based upon the fact that roentgen-ray burns, alopecia, etc., depend entirely on the quantity of a roentgen ray reaching the skin, as pointed out by Remer and Witherbee in June, 1917.<sup>1</sup>

<sup>1</sup> *Am. Jour. Roentgenol.*, June, 1917; also a more recent article published in *Arch. Dermatol. and Syphilol.*, May, 1920.

The standard formula for 1 skin unit, or the amount used for treatment of ringworm of the scalp, is expressed as follows:

$$\frac{3 \text{ sp. gr.} \times 3 \text{ ma.} \times 4 \text{ min.}}{8\text{-inch distance} \times 8\text{-inch distance}} = \frac{9}{16} = 1 \text{ skin unit.}$$

To illustrate the practical application of the above fraction  $\frac{9}{16}$ , let us take the factors given in the *Army Manual* for the various exposures, then estimate the skin distance from the target of the tube in each position of a patient whose measurements are a little above the average, substituting the skin distance in each case for the plate distance. This formula, with the skin distance substituted for the plate distance for an A. P. Head, would be:

$$\frac{5 \text{ sp. gr.} \times 40 \text{ ma.} \times \frac{1}{5} \text{ of a minute}}{12\text{-inch distance} \times 12\text{-inch distance}}$$

instead of 20-inch plate distance. This reduced to a simple fraction equals:

$$\frac{5 \times \frac{10}{3} \times \frac{1}{5}}{\frac{12}{6} \times \frac{12}{6}} = \frac{5}{18}$$

If the fraction  $\frac{5}{18}$  or its formula represents the dose for each exposure, then the number of plates taken to produce a temporary alopecia, or 1 skin unit, would be the number of times  $\frac{5}{18}$  is contained in  $\frac{9}{16}$ :

$$\frac{9}{16} \div \frac{5}{18} = \frac{9}{16} \times \frac{18}{5} = \frac{81}{40} = 2\frac{1}{40} \text{ plates.}$$

Therefore:

	Sp. gr.	Ma.	Time minutes.	Plate distance inches.	Skin distance inches.	Number of plates.
Head, A. P. . . . .	5	40	$\frac{1}{5}$	20	12	2
Head Lat. . . . .	5	40	$\frac{1}{10}$	20	14	5
Neck . . . . .	5	40	$\frac{2}{10}$	20	16	14
Shoulder . . . . .	5	40	$\frac{1}{10}$	20	10	5
Elbow . . . . .	5	40	$\frac{1}{40}$	20	17	34
Wrist . . . . .	5	40	$\frac{1}{30}$	20	18	54
Kidney . . . . .	5	40	$\frac{1}{15}$	20	10	4
Bladder . . . . .	5	40	$\frac{1}{15}$	20	12	6
Hip-joint . . . . .	5	40	$\frac{1}{12}$	20	12	5
Pelvis . . . . .	5	40	$\frac{1}{12}$	20	12	5
Knee . . . . .	5	40	$\frac{1}{30}$	20	15	19
Ankle . . . . .	5	40	$\frac{1}{40}$	20	17	34
Lumbar spine . . . . .	5	40	$\frac{1}{10}$	20	10	4
Teeth (slow film) . . . . .	5	40	$\frac{1}{15}$	20	18	13
Teeth (fast film) . . . . .	5	40	$\frac{1}{40}$	20	18	36
Chest . . . . .	5	40	$\frac{1}{15}$	28	16	11



The importance of the distance of the skin from the target of the tube is well illustrated in the list of number of plates, especially in the case of kidney and bladder exposures; here the only change in the four factors is in the distance. The difference in distance is 2 inches, which makes a difference of two in the number of plates. This should make one exceedingly cautious when dealing with excessively large individuals whose thickness demands the maximum exposure.

For one who is not using the army factors and who has inadvertently used the wrong factors in a given case to obtain the best results, and wishes to repeat the procedure, it is a simple matter to determine the dosage the skin has already received and then decide whether it would be safe to repeat or postpone the operation for a time.

In taking a series of plates or films, overlapping of the areas exposed must be considered even though the factors are correct and properly maintained throughout each exposure.

From the foregoing list of number of plates it is obvious that the head, kidney, bladder, pelvis and lumbar spine are the ones that require the larger doses to obtain results. If a case of this kind is passed on from one roentgen-ray laboratory to another, in a comparatively short time, and standard exposures made in each place, a roentgen-ray burn may occur. Roentgenologists, and especially those who specialize in the branches in which these large doses are required to obtain good plates, would appreciate a complete roentgen-ray history as well as clinical history of these cases. By a complete roentgen-ray history is meant the time the plates were taken, the position of the patient, the factors used in making the exposures and the date of the last examination. With these data the roentgenologist could determine at once how soon it would be safe to proceed with his examination, instead of waiting three or four weeks from the date of the last exposure in order to avoid either increasing an already produced burn or adding enough more to produce one that otherwise would be a safe and sane exposure.

Erythema appears in from ten to fourteen days, so that at the end of three weeks one is safe in concluding, if the skin appears normal, that the exposure the patient has had was not sufficient to produce an erythema. But the dose may have been of such intensity that by adding the large amount necessary for the second examination may induce an alopecia or erythema by the combined exposures. If an erythema or temporary alopecia has occurred during the third week after the first examination it would seem advisable to wait at least six weeks from the date of the last exposure.

From a medicolegal standpoint it would seem assured that the defendant would be in a much better position to defend himself if he knew his factors and the valuation of the same in determining the cause of roentgen-ray burns.

The army factors with an interrupterless machine and a Coolidge radiator type tube whose maximum working factors are 5-inch gap and 30 ma., would mean a change from 40 ma. to 30 ma. and a proportionate increase in the time of the exposure. For example, the factors given for an A. P. Head are 5-inch gap, 40 ma. at 20-inch distance, with 12 seconds time. To compensate for the one-quarter decrease in millimeter, the time given in army formula (12 seconds), would equal three-quarters; one-fourth would be 4 seconds and four-fourths 16 seconds, or the time necessary to produce the same effect on the plate.

The principle involved in the adaptation of the above-mentioned radiator tube to the army formula may be illustrated by Prof. J. S. Shearer's roentgenographic formula:

$$\frac{40 \text{ ma.} \times (5 \text{ K V})^2 \times \frac{1}{5} \text{ minute}}{(20\text{-inch distance})^2} = \frac{\overset{2}{10} \times \underset{4}{5} \times \underset{4_2}{5} \times \frac{1}{5}}{\underset{4}{20} \times \underset{4_2}{20}} = \frac{1}{2}$$

$$\frac{30 \text{ ma} \times (5 \text{ K V})^2 \times \text{time}}{(20\text{-inch distance})^2} = \frac{\overset{15}{30} \times \underset{4_2}{5} \times \underset{4}{5} \times T}{\underset{4_2}{20} \times \underset{4}{20}} = \frac{15}{8}$$

$$\frac{1}{2} \div \frac{15}{8} = \frac{1}{2} \times \frac{\overset{4}{8}}{15} = \frac{4}{15} \text{ minutes} = 16 \text{ seconds.}$$

By interposing  $\frac{1}{2}$  mm. aluminum filter, three times the number of plates may be made, and with 1 mm. aluminum filter six times the number of plates without danger to the patient. This is based on the time necessary to produce  $1\frac{1}{2}$  skin units of filtered roentgen ray, using  $\frac{1}{2}$  and 1 mm. aluminum filter with the army factors and skin distance instead of plate distance. From the regular formula 12 seconds is the time for one plate of an A. P. Head. With a skin distance of 12 inches  $2\frac{1}{4}$  plates can be taken without a filter. The time necessary to produce  $1\frac{1}{2}$  filtered skin units, which corresponds to  $\frac{3}{4}$  unit unfiltered biologically, using  $\frac{1}{2}$  mm. al. = about 1 minute, 12 seconds with 1 mm. al. = about 2 minutes. Therefore, 1 minute and 12 seconds = 72 seconds  $\div$  12 seconds = 6 plates, or three times the number allowed without  $\frac{1}{2}$  mm. al. filter. 2 minutes = 120 seconds  $\div$  12 seconds = 10 plates, or 5 times the number indicated without 1 mm. al. filter.

## COMPARATIVE STUDIES OF THE TOXICITY OF ARSPHENAMINE AND NEOARSPHENAMINE.

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AND

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THE growing popularity of neoarsphenamine in the treatment of syphilis, due largely to the greater ease of its administration as compared with arsphenamine, inasmuch as the solutions do not require neutralization with alkali, and may be injected with a syringe in concentrated form, renders advisable a clear conception of the relative toxicity and therapeutic activity of these compounds. The purpose of this investigation was a comparative study of the toxicity of arsphenamine and neoarsphenamine prepared by various laboratories; comparative studies of the therapeutic activity of arsphenamine and neoarsphenamine based upon their influence upon experimental trypanosomiasis in rats, is given separately.<sup>1</sup>

Numerous reports in literature by Castelli,<sup>2</sup> Hata and Hirano,<sup>3</sup> Hoke and Rihl,<sup>4</sup> Hoppe and Schreiber,<sup>5</sup> Kersten,<sup>6</sup> Kochmann,<sup>7</sup> Marschalkó and Verzprém,<sup>8</sup> Pearce and Brown<sup>9</sup> and Willcox and Webster<sup>10</sup> indicate that the highest tolerated doses of salvarsan for rabbits varies from 60 to 204 mg. per kilo, the general average being 80 to 100 mg. In a previous study reported by us<sup>11</sup> rabbits

<sup>1</sup> Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: A Comparative Study of the Trypanocidal Activity of Arsphenamine and Neoarsphenamine, *AM. JOUR. MED. SC.*

<sup>2</sup> Ueber Neosalvarsan. Bestimmung der Toxizität und der heilenden Wirkung bei experimentellen Spirochätenkrankheiten, *Ztschr. f. Chemotherapie, orig.*, 1912-1913, i, 321-352.

<sup>3</sup> Quoted by Roth: Saikin-Gaku-Zasshi, 1916, No. 244, p. 321.

<sup>4</sup> Experimentelle Untersuchungen über die Beeinflussung des Kreislaufes und der Atmung durch das Salvarsan, *Ztschr. f. Exper. Path. u. Therap.*, 1911, ix, 332-339.

<sup>5</sup> Ueber die Behandlung der Syphilis und metasypilitischen Erkrankungen mit dem neuen Ehrlich-Hataschen Arsenpräparat, *Verhandl. deutsch. Kong. f. innere Med.*, 1910, xxvii, 243-253.

<sup>6</sup> Ueber vergleichende Tierexperimente mit Salvarsan und Neosalvarsan, *Centralbl. f. Bakt., orig.*, 1912, lxx, 369-381.

<sup>7</sup> Die Toxizität des Salvarsans bei intravenöser Einverleibung nach Versuchen an Hund und Kaninchen, *München. med. Wchnschr.*, 1912, lix, 18-19.

<sup>8</sup> Histologische und experimentelle Untersuchungen ueber den Salvarsantod, *Deutsch. med. Wchnschr.*, 1912, xxxviii, 1222-1225.

<sup>9</sup> The Toxicity of Salvarsan and Neosalvarsan, *Jour. Pharmacol. and Exper. Therap.*, 1917, ix, 354-355.

<sup>10</sup> The Toxicology of Salvarsan, *British Med. Jour.*, 1916, i, 473-478.

<sup>11</sup> Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: Experimental and Clinical Studies of the Toxicity of Dioxydiaminoarsenobenzoldichlorhydrate, *Jour. Cutan. Dis.*, June, 1917.

were found to tolerate from 60 to 80 mg. of arsenobenzol per kilo of body weight over a period of several weeks; rats tolerated much larger amounts, ranging from 70 to 100 mg. per kilo. Roth<sup>12</sup> has reported that in experiments conducted in the Hygienic Laboratory rabbits were found to tolerate the various salvarsan preparations in intravenous doses of from 60 to 100 mg. per kilo of body weight for at least two weeks, although certain samples killed in doses of 60 mg. He has also corroborated our findings indicating that rats were more tolerant, amounts ranging from 60 to 135 mg. per kilo being tolerated for two weeks' period, the results depending somewhat upon whether the drugs were given in 1 or 2 per cent. solutions.

Neosalvarsan has been found much less toxic than salvarsan, the reports of Castelli,<sup>13</sup> Kersten,<sup>14</sup> Marschalkó,<sup>15</sup> Pearce and Brown,<sup>16</sup> Spiethoff<sup>17</sup> and Roth,<sup>18</sup> indicating that the tolerated dose for rabbits by intravenous injection is from 150 to 300 mg. per kilo of body weight.

**Practical Value of Toxicity Tests.** Insofar as toxicity tests with the lower animals and especially the white rats are concerned, it may be stated here that their value is limited to the detection of what may be called the "lethal toxicity" of arspenamine and neoarsphenamine; they do not exhibit the transient untoward effects observed in persons receiving intravenous injections of arspenamine and neoarsphenamine and designated as the "nitritoid crisis" or "arsphenamine reaction." The cause or causes of these reactions cannot be definitely stated at the present time; our own studies (2 and 3) have indicated that several factors may be implicated, including faulty technic in the preparation of solutions, individual susceptibility and finally the presence of an unidentified toxic substance designated as "X" in some lots of arspenamine and neoarsphenamine. Animal tests, especially in the smaller animals, fail to detect these causes of transient reactions following the administration of arspenamine and neoarsphenamine; compounds of both classes, although acceptable on the basis of "lethal toxicity tests", may still produce reactions when administered to persons. However, animal tests for "lethal toxicity" conducted by administering increasing amounts of drug by a uniform method, are of value as a means of establishing a criterion of purity and freedom from certain injurious substances and may be accepted for determining the relative lethal toxicity of arspenamine and neoarsphenamine per gram of body weight.

<sup>12</sup> An Experimental Investigation of the Toxicity of Certain Organic Arsenic Compounds, Bull. No. 113, Hygienic Laboratory, July, 1918, pp. 7-39.

<sup>13</sup> Loc. cit.

<sup>14</sup> Loc. cit.

<sup>15</sup> Ueber Neosalvarsan, Deutsch. med. Wehnschr., 1932, xxxviii, 1585-1587.

<sup>16</sup> Loc. cit.

<sup>17</sup> Experimentelle und klinische Untersuchungen mit Salvarsan-Serumlösungen. Med. Klinik, 1914, x, 584-586.

<sup>18</sup> Loc. cit.

**The Technic of Toxicity Tests.** As is now well known, many factors may modify the results of toxicity tests and especially with arspenamine administered intravenously, such as the degree of concentration of solution, the amount of alkali in the form of sodium hydroxid employed for neutralization and the rate of injection; for comparative tests the technic must be uniform and the Hygienic Laboratory has standardized the methods which may be briefly described in this place, inasmuch as the results of the studies employing rats as the test animals reported in this paper, were conducted according to these methods as follows:

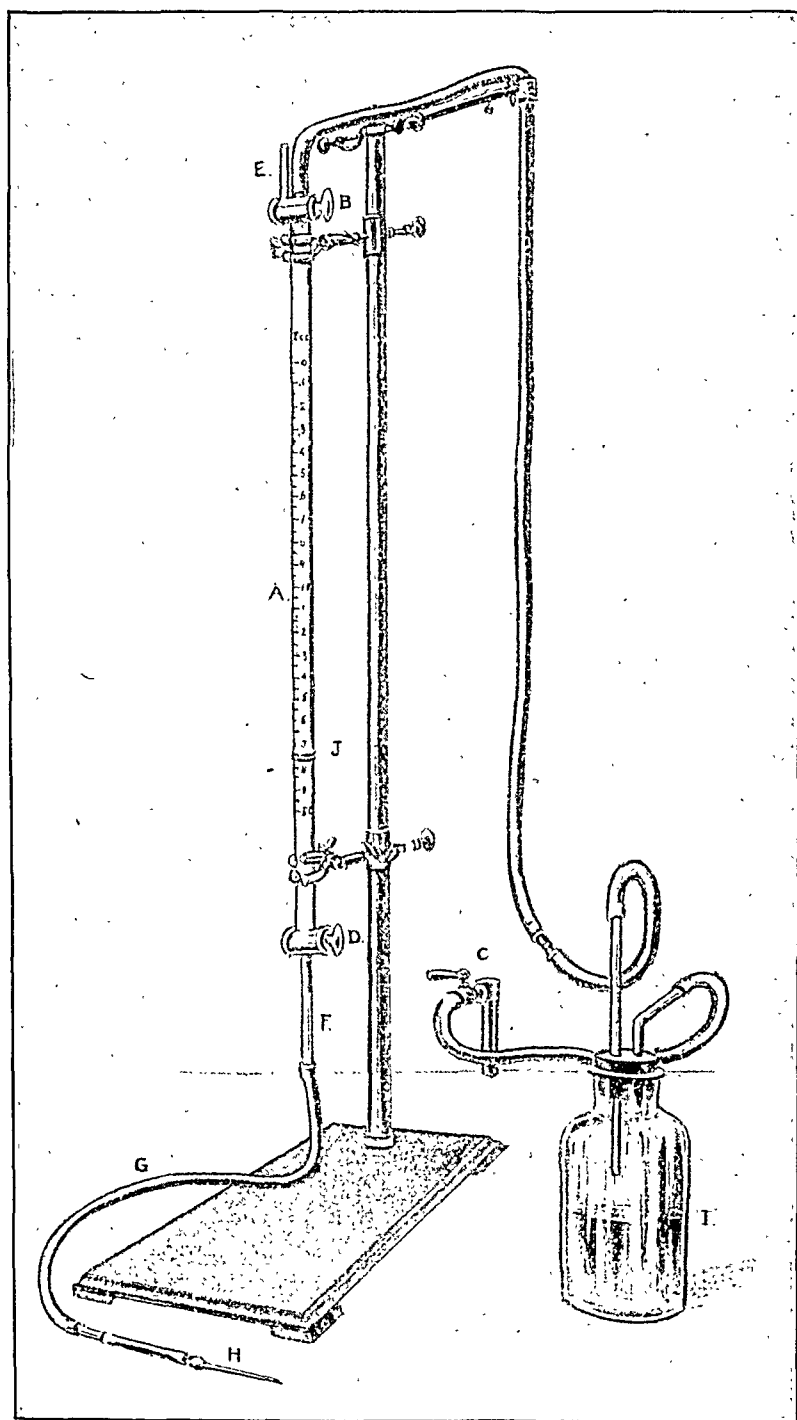
(a) *Arsphenamine Toxicity Tests.* Healthy white rats weighing for the most part between 100 and 150 gm. are employed; pregnant animals are excluded. All animals are kept under observation for at least ten to fourteen days before being used in these tests. Each animal is weighed prior to injection and the dose administered per body weight. All animals are fed late in the afternoon of the previous day in order that the weights may be taken and the injections made after a period of about eighteen hours' fasting, to render the dosage per body weight more accurate.

A 2 per cent. solution of the disodium salt of arspenamine is prepared by weighing out 0.5 gm. of powder and dissolving in 20.5 c.c. of warm, sterile, freshly distilled water; after complete solution has occurred, 4.5 c.c. of *normal* sodium hydroxide is added to convert the solution of acid base into a slightly alkaline solution of the disodium salt. Each solution is now filtered through sterile paper into a sterile vial and administered at once.

The injections are given in a saphenous vein exposed by a small incision; the gravity method is used for making the injections, employing the special apparatus designed by one of us (Kolmer), after the apparatus used by Dr. Lake in the Hygienic Laboratory. This apparatus is composed of a 2 c.c. burette divided into 0.01 c.c. (A) and fitted with a two-way cock at the upper end (B) for filling by means of suction by vacuum (C) and a water-tight cock at the lower end (D) for stopping the injection. The opening at (E) admits air to the pipette during the injection when the cock at (B) is turned after filling the pipette with solution, to cut off the vacuum. A long glass nozzle (F) is attached to the burette fitted with a short piece of best grade rubber tubing (G) carrying a window near the end, and a needle of No. 26 to No. 22 gauge (H).

Before injecting this solution the needle and rubber tubing are sterilized by boiling and the burette cleansed by copious flushing by means of the vacuum suction with sterile water followed by the solution to be injected, the water and solution of arspenamine collecting in the bottle (I) interposed between the vacuum and the burette. When solutions are changed the apparatus is cleansed between each in the same manner.

After the animal is bound upon the operating board the skin of the anterior surface of the thigh is cleansed with alcohol and a



small incision made over the vein, which is rendered prominent by pressure made in the inguinal region by an assistant. The vein

is grasped with fine forceps, due care being taken not to produce pain by grasping the nerve alongside of the vein, the needle is inserted and the cock (*D*) gradually opened to regulate the flow while the time in seconds is called off by an assistant, until the dose to be given previously marked off by the rider (*J*) fastened to the burette, is injected.

With this apparatus it is possible to inject a given amount of solution very accurately and at a given rate of flow set down by the Hygienic Laboratory at 0.5 c.c. per sixty seconds; the amount of solution to be injected is calculated according to the dose to be given per 100 gm. of weight and the rate of injection can be nicely regulated by means of the stop cock at (*D*) and timed with a stop clock. The apparatus is to be recommended for the intravenous injection of rats, guinea-pigs and rabbits, when a definite rate of flow is required in the conduct of toxicity tests with arspenamine, tuberculin and various other drugs.

In conducting the toxicity tests the weight and sex of each rat is recorded, as likewise the dose of drug per kilogram of body weight, the amount of 2 per cent. solution carrying this dose and the actual time in seconds required for making the injection, as shown in Table I.

The animals are kept under observation for two weeks, although the official test is concluded at the expiration of forty-eight hours following injection. The Hygienic Laboratory requires the injection of at least six rats with a dose of 0.100 gm. each per kilogram of body weight; at least four of these animals (75 per cent.), must survive for two days.

(b) *Neoararsphenamine Toxicity Tests.* Tests for the toxicity of neoarsphenamine are conducted in exactly the same manner except that the doses per kilogram of weight are larger, 4 per cent. solutions in sterile distilled water are injected and the vein is tied after injection to prevent bleeding, inasmuch as the coagulation time of the blood is lowered.

In preparing the solutions we dissolve 0.8 gm. in 20 c.c. cold sterile, distilled water and filter the solution through sterile paper; the animals are kept under observation for fourteen days. The Hygienic Laboratory requires that 75 per cent. of animals receiving 0.200 gm. per kilogram shall survive for at least seven days.

Additional tests have been conducted by us by subcutaneous injections of mice and rats with solutions of arspenamine and neoarsphenamine, this being the method of conducting these toxicity tests in Germany. These injections were made under the skin of the back. Owing to the great irritation produced by these compounds and particularly arspenamine, ulcers were occasionally produced and the results were seldom as sharp and clear cut as those following intravenous injections; furthermore, the intravenous route is preferable by reason of the fact that both arspenamine

and neoarsphenamine are commonly administered by this route in the human subject.

**Scope of Investigation.** In conducting this investigation arsphenamine and neoarsphenamine from six different laboratories designated by the numerals 1, 2, 3, 4, 5 and 6, were tested. Increasing amounts of these compounds were administered to rats by intravenous and subcutaneous injection, and to mice by subcutaneous injection. In each experiment the technic was identical in order to elicit the differences in toxicity of arsphenamine and neoarsphenamine due to the solutions of the drugs themselves.

**Results.** The results of toxicity tests conducted by intravenous injection of rats with arsphenamine and neoarsphenamine are shown in Tables I, II and III; Table I is a record of the results observed and Tables II and III summarize the results of these tests by stating the largest amounts of arsphenamine and neoarsphenamine tolerated over a period of seven days.

TABLE I.—TOXICITY OF ARSPHENAMINE AND NEOARSPHENAMINE BY INTRAVENOUS INJECTION IN RATS.

No.	Wt., gms.	Sex.	Compound.	Dose per kilo.	Amount injected c.c.	Time of injection seconds.	Results in days.			
							At once.		2	3
1	125	M.*	Arsphenamine (Lab. No. 2)	0.08	0.50	60	—†	—	—	—
2	120	M.		0.08	0.48	57	—	—	—	—
3	95	F.		0.09	0.43	52	—	—	—	—
4	100	F.		0.09	0.45	54	—	—	—	—
5	80	M.		0.10	0.40	48	—	—	—	—
6	75	M.		0.10	0.38	45	—	—	—	—
7	85	M.		0.11	0.46	55	—	D.	—	—
8	95	M.		0.11	0.52	62	—	—	—	—
9	85	M.		0.12	0.51	61	—	D.	—	—
10	80	M.		0.12	0.48	57	—	—	—	—
11	115	M.	Neoarsphenamine (Lab. No. 2)	0.20	0.58	69	—	—	—	—
12	135	M.		0.20	0.68	82	—	—	—	—
13	125	M.		0.22	0.69	83	—	—	—	—
14	90	M.		0.22	0.50	57	—	—	—	—
15	105	M.		0.25	0.66	79	—	—	—	—
16	125	M.		0.25	0.78	94	—	—	—	—
17	85	M.		0.28	0.60	72	—	—	—	—
18	140	M.		0.28	0.98	118	—	—	—	—
19	115	M.		0.30	0.86	103	—	—	—	—
20	75	M.		0.30	0.56	67	—	D.	—	—

\* M., male; F., female.

† Lived; D., died.

Tables IV and V represent the results observed with subcutaneous injections of solutions of arsphenamine and neoarsphenamine given to rats and mice; a summary of the results of tests of this kind is presented in Table VI.



TABLE II.—TOXICITY OF ARSPHENAMINE BY INTRAVENOUS INJECTION IN RATS.

Compound.	Highest dose per kilogram of weight tolerated for seven days.								Average.
	Exper. 1.	Exper. 2.	Exper. 3.	Exper. 4.	Exper. 5.	Exper. 6.	Exper. 7.	Exper. 8.	
Lab. No. 1 . . . .	0.11 more than	0.10 more than	0.09	..	..	..	..	..	0.100
Lab. No. 2 . . . .	0.12	0.12	0.10	0.10	0.10	0.10	0.10	0.10	0.105+
Lab. No. 3 . . . .	0.12 more than	0.10	0.10	..	..	..	..	..	0.106
Lab. No. 4 . . . .	0.12	0.10	0.10	0.11	..	..	..	..	0.105+
Lab. No. 5 . . . .	0.11	0.12	0.10	..	..	..	..	..	0.110
Lab. No. 6 . . . .	0.10	..	..	..	..	..	..	..	—

TABLE III.—THE TOXICITY OF NEOARSPHENAMINE BY INTRAVENOUS INJECTION IN RATS.

Compound.	Highest dose per kilogram of weight tolerated for seven days.										Average.
	Exper. 1.	Exper. 2.	Exper. 3.	Exper. 4.	Exper. 5.	Exper. 6.	Exper. 7.	Exper. 8.	Exper. 9.	Exper. 10.	
Lab. No. 1 . . . .	0.28 more than	0.20 more than	0.18	0.25	..	..	.. more than	..	.. more than	..	0.228
Lab. No. 2 . . . .	0.30	0.30	0.28	0.28	0.22	0.25	0.30	0.225	0.30	0.28	0.278+
Lab. No. 3 . . . .	0.28	0.22	0.25	..	..	..	..	..	..	..	0.250
Lab. No. 4 . . . .	0.20	0.25	0.28	..	..	..	..	..	..	..	0.243
Lab. No. 5 . . . .	..	..	..	more than	..	..	..	..	..	..	0.270+

TABLE IV.—TOXICITY OF ARSPHENAMINE AND NEOARSPHENAMINE BY SUBCUTANEOUS INJECTION IN RATS.

No.	Wt., gms.	Sex.	Compound.	Dose per kilo. gms.	Amount of solu- tion injected, c.c.	Results in days.							
						At once.	1	2	3	4	5	6	7
1	95	F.	Arsphenamine (Lab. No. 2)	0.533	1.7	—	—	—	—	—	—	—	—
2	110	M.		0.533	2.0	—	D.	—	—	—	—	—	—
3	115	M.		0.400	1.57	—	—	—	—	—	—	—	—
4	100	M.		0.400	1.36	—	D.	—	—	—	—	—	—
5	120	M.		0.200	1.0	—	—	—	—	—	—	—	—
6	140	M.		0.200	1.0	—	—	—	—	—	—	—	—
7	160	M.		0.133	1.0	—	—	—	—	—	—	—	—
8	250	M.		0.133	1.1	—	—	—	—	—	—	—	—
9	195	M.		0.066	1.0	—	—	—	—	—	—	—	—
10	145	M.		0.066	1.0	—	—	—	—	—	—	—	—
11	115	M.	Neoarsphenamine (Lab. No. 2)	0.533	2.3	—	D.	—	—	—	—	—	—
12	150	M.		0.533	2.0	—	D.	—	—	—	—	—	—
13	90	M.		0.400	1.3	—	—	D.	—	—	—	—	—
14	115	M.		0.400	1.7	—	D.	—	—	—	—	—	—
15	140	M.		0.200	1.0	—	—	—	—	—	—	—	—
16	105	M.		0.200	0.5	—	—	—	—	—	—	—	—
17	90	F.		0.133	0.5	—	—	—	—	—	—	—	—
18	175	F.		0.133	0.5	—	—	—	—	—	—	—	—
19	210	M.		0.066	0.5	—	—	—	—	—	—	—	—
20	190	M.		0.066	0.5	—	—	—	—	—	—	—	—

TABLE V.—TOXICITY OF ARSPHENAMINE AND NEOARSPHENAMINE BY SUBCUTANEOUS INJECTION IN MICE.

No.	Wt., gms.	Compound.	Dose per kilo. gms.	Amount of solution injected, c.c.	Results in days.							
					At once.	1	2	3	4	5	6	7
1	22	Arsphenamine (Lab. No. 2)	0.533	0.5	—	D.						
2	20		0.533	0.5	—	D.						
3	21		0.400	0.5	—	—	—	—	—	—	—	D.
4	19		0.400	0.5	—	D.						
5	19		0.200	0.5	—	—	—	—	—	—	—	—
6	23		0.200	0.5	—	—	—	—	—	—	—	—
7	22		0.133	0.5	—	—	—	—	—	—	—	—
8	22		0.133	0.5	—	—	—	—	—	—	—	—
9	17		0.066	0.5	—	—	—	—	—	—	—	—
10	18		0.066	0.5	—	—	—	—	—	—	—	—
11	22	Neoarsphenamine (Lab. No. 2)	0.533	0.5	—	D.						
12	18		0.533	0.5	—	D.						
13	13		0.400	0.5	—	—	—	—	—	—	—	—
14	23		0.400	0.5	—	—	—	—	—	—	—	—
15	22		0.200	0.5	—	—	—	—	—	—	—	—
16	17		0.200	0.5	—	—	—	—	—	—	—	—
17	18		0.133	0.5	—	—	—	—	—	—	—	—
18	16		0.133	0.5	—	—	—	—	—	—	—	—
19	22		0.066	0.5	—	—	—	—	—	—	—	—
20	18		0.066	0.5	—	—	—	—	—	—	—	—

TABLE VI.—TOXICITY OF ARSPHENAMINE AND NEOARSPHENAMINE BY SUBCUTANEOUS INJECTION IN MICE AND RATS.

Compound.	Animal.	Highest dose per kilogram tolerated for seven days.							Average.
		Exper. 1.	Exper. 2.	Exper. 3.	Exper. 4.	Exper. 5.	Exper. 6.	Exper. 7.	
Arsphenamine	Mouse	0.20	0.13	0.20	0.200	0.07	0.070	0.130	0.143
Neoarsphenamine	Mouse	0.20	0.40	0.20	0.330	0.33	0.400	0.200	0.286
Arsphenamine	Rat	0.20	0.40	0.40	0.200	0.20	0.460	0.533	0.342
Neoarsphenamine	Rat	0.20	0.20	0.20	0.133	0.20	0.133	..	0.177

A general summary of the results of this investigation is given in Table VII showing the highest, lowest and average dose of arsphenamine and neoarsphenamine per kilogram of body weight tolerated by mice and rats by subcutaneous and intravenous injection.

TABLE VII.—SUMMARY SHOWING COMPARATIVE TOXICITY OF ARSPHENAMINE AND NEOARSPHENAMINE.

Compound.	Animal.	Route of injection.	Tolerated doses per kilo in seven days.		Average.
			Highest.	Lowest.	
Arsphenamine . . .	Mouse	Subcutaneous	0.20	0.07	0.143
Neoarsphenamine . . .	Mouse	Subcutaneous	0.40	0.20	0.286
Arsphenamine . . .	Rat	Subcutaneous	0.40	0.20	0.342
Neoarsphenamine . . .	Rat	Subcutaneous	0.20	0.13	0.177
Arsphenamine . . .	Rat	Intravenous	0.12	0.09	0.105
Neoarsphenamine . . .	Rat	Intravenous	0.30	0.18	0.254

**Summary.** These results may be summarized as follows:

1. Arsphenamine when injected intravenously in rats in the form of 2 per cent. solutions of the disodium salt in water after the method described, is generally borne in an amount averaging 0.105 gm. per kilogram of body weight corresponding to 7.35 gm. for a person weighing seventy kilograms or about one hundred and fifty pounds and representing an amount twelve times greater than the maximum dose (0.6 gm.) given at one time to an adult in the treatment of syphilis. The products of the different laboratories chosen at random for this study, were closely similar in toxicity; the range of tolerance over a period of seven days was from 0.090 to 0.120 gm. per kilogram of weight. Some lots of arsphenamine are tolerated by rats in larger amounts ranging to 0.150 gm. and even higher per kilogram of weight, but the average highest tolerated dose with arsphenamine dispensed at the time these studies were made appeared to be between 0.100 and 0.110 gm. per kilo. As previously stated, the Hygienic Laboratory requires that arsphenamine be borne by rats for two days in 0.100 gm. per kilogram of weight, and this appears to be a sufficiently high standard of purity.

2. Neoarsphenamine when injected intravenously into rats in a 4 per cent. solution in water is borne for seven days in doses varying from 0.180 to 0.300 gm. or more per kilogram of body weight; the average tolerance is about 0.254 gm. per kilogram of body weight which is equivalent to about 17.5 gm. for a person weighing seventy kilograms and about nineteen times more than the maximum dose (0.9 gm.) given in one injection in the treatment of syphilis. The Hygienic Laboratory requires that neoarsphenamine pass animal tests at 0.200 gm. per kilo of body weight over a period of seven days. Inasmuch as the toxicity of different lots of the compound varies considerably owing to the intricate chemical processes of manufacture, this would appear to be a fair index of purity for these compounds.

3. By intravenous injections in rats, neoarsphenamine is therefore about 2.4 times less toxic than arsphenamine:

$$\frac{\text{Average tolerated dose of neoarsphenamine, 0.254 gm. per kilo}}{\text{Average tolerated dose of arsphenamine, 0.105 gm. per kilo}} = 2.4$$

Taking 0.6 gm. arsphenamine and 0.9 gm. neoarsphenamine as the dose administered to adult persons in the treatment of syphilis, this dose of arsphenamine represents an amount twelve times less than the highest average tolerated dose for the rat and of neoarsphenamine nineteen times less than the highest average dose. If the results of these toxicity tests on rats can be applied to persons it is therefore evident that doses of neoarsphenamine greater than 0.9 gram may be given and yet remain within the same range of safety as the 0.6 gm. dose of arsphenamine.

4. Curiously arspenamine is borne in larger doses than neoarsphenamine when injected into rats subcutaneously. Arspenamine was tolerated in doses ranging from 0.200 to 0.533 gm. per kilogram of body weight with an average of 0.342 gm.; neoarsphenamine was tolerated in doses varying from 0.133 to 0.200 gm. per kilogram of weight with an average of but 0.177 gm.

5. When injected subcutaneously in mice arspenamine was tolerated in amounts ranging from 0.070 to 0.200 gm. per kilogram of body weight averaging 0.143 gm.; neoarsphenamine was tolerated in doses ranging from 0.200 to 0.400 gm. averaging 0.286 gm. Castelli<sup>20</sup> found that while mice tolerated 0.143 gm. salvarsan and 0.250 gm. neosalvarsan when injected intravenously, the degree of tolerance was reversed when the compounds were injected subcutaneously, the tolerated doses being 0.250 gm. salvarsan and but 0.085 gm. neosalvarsan per kilogram of weight. Our results with a few experiments employing mice did not confirm these findings although with rats we found a reversal in tolerance similar to the results observed by him with mice.

6. Castelli also tested the toxicity of salvarsan and neosalvarsan for the hen, pigeon and rabbit, a summary of his results being given in Table VIII; many of our tests for the toxicity of arspenamine made several years ago were conducted by injecting rabbits intravenously with a piston syringe, the total amount of fluid injected being 10 c.c., and given at a rapid rate into the ear vein. With this technic we found the toxicity of arspenamine at this time for rabbits to be in the neighborhood of 0.080 gm. per kilogram of body weight indicating that the smaller animal (such as the rat) tolerates these arsenical compounds proportionate to weight better than the larger animal (rabbit). It is of interest to note that Castelli's results are similar, inasmuch as mice tolerated larger doses per kilogram of weight than rabbits.

TABLE VIII.—THE TOXICITY OF SALVARSAN AND NEOSALVARSAN AFTER CASTELLI.

Animal.	Route of administration.	Dosis tolerata per kilogram.	
		Salvarsan.	Neosalvarsan.
Mouse . . . .	{ Intravenous	0.143	0.250
	{ Subcutaneous	0.250	0.085
Hen . . . .	{ Intravenous	0.080	0.060
	{ Intramuscular	0.250	0.010
Pigeon . . . .	{ Intravenous	0.080	0.120
	{ Intramuscular	0.090	0.040
Rabbit . . . .	{ Intravenous	0.100	0.200
	{ Subcutaneous	0.150	0.100

**Conclusions.** 1. Toxicity tests of arspenamine and neoarsphenamine among the lower animals possess definite practical

<sup>20</sup> Loc cit.

value as a means of establishing standards of purity for these compounds.

2. These toxicity tests are best conducted by injecting solutions of the drugs intravenously inasmuch as this is the usual method of administration in the treatment of syphilis and the results are sharper than observed with subcutaneous injections.

3. Animal tests show "lethal toxicity" only, that is, the duration of life after the administration of given amounts per gram of body weight; they do not give rise to the transient untoward effects of arsphenamine and neoarsphenamine ascribed to faults of technic in the preparation and injection of the solutions and the presence of an unidentified toxic substance designated as "X," which we believe may be present in the compounds themselves and produce the "nitritoid crisis."

4. The highest tolerated doses of arsphenamine and neoarsphenamine administered by intravenous injection to healthy rats are about 0.105 and 0.254 gm. per kilogram of body weight respectively; neoarsphenamine is therefore about 2.4 times less toxic than arsphenamine. Calculated upon the basis of seventy kilograms as the body weight of an average person, the highest tolerated dose of arsphenamine may be placed at 7.35 gm. and of neoarsphenamine at 17.5 gm., providing the tissues of persons are approximately of the same susceptibility; comparative tests among rabbits, rats and mice in which the same amounts of drugs were given per gram of body weight indicate, however, that the larger and heavier animals are more susceptible and very probably human subjects cannot tolerate these substances in doses proportionate to body weight as established in animals.

5. By subcutaneous injection in mice neoarsphenamine was found to be half as toxic as arsphenamine but when administered subcutaneously to rats, neoarsphenamine was found twice as toxic as arsphenamine.

6. Insofar as the toxicity of arsphenamine and neoarsphenamine, may be determined by intravenous injection of solutions in rats, the single dose of arsphenamine commonly administered (0.6 gm.) may be said to be about twelve times less than the highest tolerated dose and the highest single dose of neoarsphenamine commonly injected (0.9 gm.) is about nineteen times less; from the standpoint of margin of safety larger amounts of neoarsphenamine may be given and maintain the same ratio between *dosis therapeutica* and *dosis tolerata*, as apparently exists with arsphenamine.

## A BRIEF EXPERIENCE WITH APPENDICOSTOMY AND CECOSTOMY FOR INTESTINAL STASIS IN EPILEPSY AND NEURASTHENIA.<sup>1</sup>

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I HAVE had an opportunity in the last year or two to observe a small group of patients—two with neurasthenic symptoms and two with epilepsy—who had a considerable degree of intestinal stasis and in whom appendicostomy or cecostomy was done with subsequent washing out of the large intestine for a period of six to twenty-six months. The operation was done on the theory that delay in the passage of the contents of the colon and possible absorption of toxic material was responsible for some or all of these symptoms, and that the patient would be relieved by keeping the bowel well cleaned out.

The patients had all had a long, thorough course of medical treatment under the best conditions; some of them had stayed for a year or more at one of our best sanitariums, with little or no improvement of symptoms, and the operation was only done as a last resort. They were all patients seen in consultation and had been considerably encouraged by other physicians, who had seen them, to have the operation performed. Personally I did not have much enthusiasm for the method, but I was placed in a fortunate position to be able to follow the cases and to observe the results of the operation and subsequent treatment.

The literature of the subject is rather scanty and confusing. We are very likely to find immediate good results reported and the late results not given. Naturally the late results are chiefly interesting.

These cases, though few in number, are reported largely to stimulate discussion and bring out the experience of other men at this meeting. It seems worth while to have the facts in these cases even if the results are not brilliant.

**Symptoms and Signs.** The two epileptic cases gave a typical history of epileptic attacks of long duration, namely, fourteen years. The other two cases had pronounced chronic neurasthenic symptoms, headaches, insomnia, attacks of indigestion, anorexia, loss of weight, poor circulation, fatigue, mental apathy, bad taste in the mouth, abdominal gas, occasional tenderness, some staining of the skin, etc. They were all habitually constipated and had a palpable "juicy" cecum, and a roentgen-ray examination showed considerable delay in the passage of barium and food material.

<sup>1</sup> Read at the Twenty-second Annual Meeting of the American Gastro-enterological Association, Atlantic City, June 10, 1919.

through the large intestine, so that at the end of two days there was still a good-sized residue throughout the colon. All were slow in emptying the right side of the colon. We realize that intestinal stasis is not a perfectly definite diagnosis; that the normal bowel schedule varies a good deal; that individuals may be in apparent perfect health and have very different rates of emptying the colon. We also know there is a good deal of normal variation in the same patient at different times. These patients, however, emptied the large intestine habitually at a much slower rate than the average normal person.

**Selection of Cases.** It is a difficult matter to select proper cases of this type for operation when we are dealing with neurasthenic or neuromental or epileptic patients who are also constipated. We have a good deal of difficulty in deciding which condition is primary—in short, whether they are constipated, because they are weak, neurotic and unstable and have low, intestinal tone, due to fatigue, worry and distress; or whether the reverse is true, namely, that they have neuromental symptoms because they are constipated and are being more or less poisoned by intestinal absorption; or whether possibly we have a vicious circle which it is wise to break at whatever point we can.

We must emphasize once more that a long, thorough medical treatment under the best conditions should precede any thought of surgical methods. This medical treatment will include rest cure, psychotherapy, exercises, diet, the use of oil, agar and suitable drugs.

Since it is difficult to pick out the neurasthenic or epileptic whom we feel sure that intestinal surgery will help, we must, of course, condemn the indiscriminate use of surgery in such cases. The cause of epilepsy in particular is very complex. Many of the factors which are believed to cause epilepsy are not peculiar to it. We commonly find every one of the lesions which are associated with epilepsy in other people without epileptic symptoms, and while abnormal conditions of the bowel are probably important in causing attacks in some epileptics we have no evidence that this is true of all epileptics. The roentgen ray often shows changes in the intestinal tract in epileptics like those found frequently in non-epileptic. We find intestinal stasis, ptosis, etc., but we must remember that while all epileptics are constipated very few constipated people have epilepsy.

Many methods of relieving epilepsy have been used at various times in the world's history and later discarded as useless. Is this another?

Other things being equal, the greater the delay in emptying the colon the more suitable these cases are for surgery, but colon stasis is far from being the only factor to consider. The operation of cecostomy or appendicostomy is probably justified in carefully selected cases, but it is largely experimental at present, and I believe this should be explained to the patient.

**Operation.** We shall not discuss at length the kind of operation best suited to such patients. We know that only a fraction of 1 per cent. of cases of intestinal stasis are obstructive or organic, the rank and file are functional, atonic and ptotic, and, therefore, appendicostomy or cecostomy was chosen for these patients in preference to colectomy, because they are much simpler operations and more suited to the simpler type of non-obstructive case. They are free from the objections of the short-circuiting operations and are far less serious than a right colectomy.

There are some purely local after-effects of this type of operation which may be important in neurotic and sensitive persons. There is often a disagreeable amount of fatigue and disability in a nervous woman from any operation whatever, which may last for weeks or months. In addition any colostomy may be disagreeable, there may be some local irritation, a little pus discharge about the wound, slight odors, some local pain at first so they cannot walk about, all of which are disagreeable to a sensitive woman. The after-effect must be good enough to overcome all these features.

**Results.** The actual results of the operation and subsequent lavage are difficult to judge in this class of patients; the firm belief of the patient that something definite is being done to help him has a marked effect, which is purely psychic, and we must also remember that a remission of epileptic attacks may follow any surgical operation of whatever sort.

The immediate effects of the operation were not important in most of the cases and the convalescence was reasonably prompt and easy. In one neurasthenic patient the immediate effects were trying. For several months after the operation she was very nervous and tired, and there was considerable local irritation from the wound which prevented walking about.

The late results have been as follows: Both neurasthenic patients considered the operation a real help; in one a definite improvement in symptoms, such as headache, dulness and fatigue, occurred; intestinal gas, formerly very troublesome, almost disappeared; sleep improved; attacks of depression disappeared. In the other neurasthenic case, while the operation was very simple and easy and convalescence rapid, the end-result was not satisfactory. The patient had many nervous and mental symptoms and could not be said to be really improved at all in spite of the fact that the irrigation was very simple and easy and thorough, and in this patient the mental condition was for a time precarious. After ten months the patient complained much of discomfort in the neighborhood of the opening and also from the dressings, so the appendix was removed and the abdomen closed. Her mental condition has continued to improve slowly under careful sanitarium treatment.

The results in the epileptic cases were as follows: In the first patient (Case III), who has also chronic nephritis and who had



been having attacks three or four times a year, the attacks entirely stopped for a period of eight months after the operation. Since that time they have occurred again in a slightly milder form than before and rather more frequently than before; the two attacks in the last six months have been very mild. (See diagram.)

	Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1916 . .	..	X	..	X	..	..	..	X				
1917 . .	..	..	..	X	..	..	XX	..	X	Operation		
1918 . .	..	..	..	..	..	X	X	X	X		X	
1919 . .	..	X	X X	..	X	..	..	X	..	..	X	

X represents an attack.

The other epileptic patient, a more serious case, in whom the attacks were frequent and severe before operation, averaging one to two a month, had no attacks for two months after operation then the attacks continued just as often as before, though some were not as severe.

There have been no marked changes in physical signs in any of these cases, except that one patient gained 15 pounds. Two patients were recently examined to see if the action of the colon had become more prompt and satisfactory than before operation. We tried to judge of this by a roentgen-ray examination, and it was found that, when examined at the end of thirty-six hours, the food and barium had made better progress through the intestine than before the operation, and that the right side of the colon was much better emptied out. Both patients, however, were somewhat behind the average normal schedule for emptying the colon. Of course, the daily irrigation was omitted at the time these barium tests of motility were made. We have considered the shape of the bowel of little importance compared with its function. We agree with Cannon that "Handsome is as handsome does."

I am left with somewhat mixed feelings at the end of these observations. All the patients feel they have been helped and are glad that the operation was performed. One neurasthenic case is definitely better now than before. This is not true of the other neurasthenic case.

The results in the epileptic cases were rather striking for a time, but we find the patients at the end of one to one and a half years in a condition which is much like that before operation. In looking over the literature and talking with various men it seems that we may expect an occasional brilliant result in such cases, perhaps one in ten, depending on the selection of patients; that toxemia will be removed; that changes in intestinal bacteriology will occur and the intestinal muscles and mucous membrane and secretion will be-

improved. On the other hand in many or most such cases we shall get little or no result. In epilepsy we do not change the neurological make-up of the patient, we simply remove a contributing cause not a primary one.

In Gant's<sup>2</sup> series of about 200 cases of appendicostomy or cecostomy, chiefly for colon infections, only 2 cases of epilepsy were treated. They were relieved, but attacks recurred in two to six months. Brewster,<sup>3</sup> at the Massachusetts General Hospital, in a series of twelve similar cases of epilepsy and colon stasis, using a bigger operation, right colectomy, reports that while the general condition of most of the cases improved, and they were largely relieved of their constipation, there was slight if any change in the epileptic attacks. I have not found one considerable series of cases in the literature in which uniform benefit has been reported by a reliable man. In talking with those in charge of the well-known colonies for epileptics in Massachusetts and New York I do not find much enthusiasm for this kind of treatment. Their few epileptics, with appendicostomy and daily lavage, have not received any more benefit than might be expected from the use of ordinary irrigations at regular intervals.

It is difficult to decide when to close the opening; in two of our cases it was closed in six and ten months respectively, because of local discomfort and because nothing seemed likely to be gained by keeping it open and continuing the irrigations longer. In the two other cases it remains open (January, 1920) nineteen and twenty-seven months after operation. It is, of course, possible to test the probable effect of closing the opening at any time by simply stopping the irrigations for a period and watching the result.

Since following this small group of cases I have seen several patients with definite epilepsy associated with definite atonic delay in the colon and have hesitated to advise any operation on the colon. I have, also, several neuropathic persons under observation at present with marked degrees of non-obstructive intestinal stasis, and even after long and only partially successful medical treatment I have hesitated to advise even the simple operations which we have been considering.

**Conclusions.** In summing up we may say that all our patients were glad that the operation was done; one neurasthenic patient was definitely and permanently improved and one was not. In both epileptic cases the immediate results were fair or good (two to eight months without attacks). The late results were unsatisfactory. I have hesitated to advise operation in later similar cases in both groups.

Constipation is so frequent in neurasthenics and epileptics that

<sup>2</sup> Diarrheal inflammatory and Parasitic Intestinal Diseases, Philadelphia, 1915.

<sup>3</sup> Ann. Surg., 1918, lviii, 203.

we are tempted by the theory that their symptoms are due to intestinal stasis and toxemia. On the other hand it is too much to expect that we can change the character of these patients by operation and lavage without help on their part. We may remove a contributing cause, but not a primary one.

We shall always have difficulty in selecting patients for such operations, because we shall often be in doubt, which condition is primary, the stasis or the nervous condition, and we usually advise operation to break into a vicious circle and to remove a contributing cause.

The question of when to close the colotomy is also difficult to decide.

We feel quite doubtful about extending surgical treatment to any non-obstructive colon stasis case (unless we have stasis of one hundred hours or more). If we do, the operation must not be risky and must give relief without troublesome complications. Such operations are largely experimental at present.

CASE I.—Miss M. A. D., aged thirty-one years. Diagnosis: neurasthenia, abdominal ptosis and marked colon stasis without obstruction.

Mother neuropathic; one brother chronic alcoholism.

Pulmonary tuberculosis at sixteen, which was arrested; average health; active; athletic until seven years ago, since then anorexia; epigastric distress or pain; occasional vomiting; frequent regurgitation of food; chronic constipation; headache; fatigue; insomnia; irritability and depression.

*Physical Examination.* Long; thin; nothing abnormal in heart or lungs; gastric secretion variable; marked abdominal atony and ptosis. Stomach reached four inches below the naval. The colon entirely below the navel. Stomach and small intestine emptying normally. Seventy-six-hour uniform colon stasis without obstruction found on several examinations. Feces no important changes.

Much sanitarium treatment for years: diet, rest, exercise, abdominal massage, oil, agar, with little improvement.

Appendicostomy, February, 1918. Dr. D. F. Jones, of Boston. Rapid recovery from operation; irrigation of colon twice a day at first, later once a day for ten months; no important changes in nervous or digestive symptoms; mental condition precarious; somewhat stronger physically; steady gain in weight of fifteen pounds. Patient is glad the operation was done. At the end of ten months considerable discomfort near the opening, so that the appendix was removed and the abdomen closed. Her mental condition has continued to improve slightly under sanitarium treatment (one and one-half years after operation, under Dr. F. X. Dercum, Philadelphia).

CASE II.—Miss E. L., aged thirty years. Diagnosis: neurasthenia, ptosis, colon stasis, atonic type. Father and mother and

two brothers and two sisters well; one sister had chronic headache; one brother mental.

Athletic, very active, repeated tonsillitis, tonsillectomy at age of fourteen. Eight years fatigue, depression, insomnia, intestinal indigestion, constipation, distress, gas. Chronic appendix and uterine fibroid removed five years ago. No improvement of the digestive symptoms. Best weight, 130 pounds; loss to 110 pounds, gained again to 120 before operation.

*Physical Examination.* Small, muscular, sallow, pigmented skin; gastric secretion, low normal. Feces, nothing abnormal. Stomach, slight ptosis (two inches); marked ptosis in right half of colon; redundant hepatic flexure, moderate adhesions at tip of cecum; no ileal stasis; marked forty-eight-hour stasis in colon, not obstructive; tip of cecum remains filled after emptying ascending and transverse colon.

Much sanitarium treatment, rest, diet, exercise, abdominal massage, oil, agar, enemata. Recent gain of 10 pounds in weight, little change in nervous or digestive symptoms.

June, 1918, cecostomy. Dr. G. W. W. Brewster, Boston. Lavage daily for five months, then every day or two, and one year later every second day; had stool only with irrigation; was very tired and nervous for several months after operation; also had local irritation in wound, so that she could not walk about very much for four or five months. Patient thinks the operation was worth while and has been glad to suffer the discomfort of it for the sake of what improvement has followed. Sleep is good. There is less fatigue, with no depression. The head is clearer, which the patient considers "a great improvement." The patient is not strong but enjoys life and works quite steadily part of each day. No further gain in weight. Roentgen-ray examination of the bowel a year after operation shows the right half of the colon well filled twenty-four hours after a barium meal. This is quite well cleared out by irrigation. Position and mobility of right colon the same. (Cecostomy still open nineteen months after operation, January, 1920.)

CASE III.—Mr. W. B. P., aged fifty-two years; draftsman. Diagnosis: epilepsy; chronic nephritis, with hypertension; colon stasis. Was referred to me by Dr. W. G. Morgan, of Washington, after operation one and a half years ago. I have followed him for sixteen months.

Family history good; two healthy children; athletic; always constipated; had piles. Epileptic attacks usually nocturnal, began fourteen years ago at the age of thirty-seven; had two or three a year; strong; good sleep; no headache, treated by low proteid diet and bromides for years.

Well-developed and nourished; good color; blood-pressure: systolic, 155 to 210; diastolic, 105 to 125; pulse, 82; three or four

premature beats per minute; moderate enlargement of heart; systolic murmur over the whole precordia; sulphonephthalein test of the kidney 55 per cent. in two hours. Urine, 1600 c.c.; specific gravity, 1009; albumin one-eighth to one-fourth per cent.; no sugar; scanty sediment; few hyalin and granular casts and renal cells.

Roentgen-ray examination showed that stomach and small intestine emptied normally, marked ptosis and spasm of the colon resulting in forty-eight-hour marked cecal stasis; no adhesions.

Appendicostomy, October, 1917. Daily lavage of colon; stopped work for one year; attacks (see chart); formerly three a year; stopped entirely for eight months. In the following year there were nine, all mild, and in the last six months two attacks, both very mild. Feels well except for attacks. Bowels move normally with irrigation. Several recent roentgen-ray examinations of the bowel, nineteen months after operation (omitting irrigation), showed that the right half of the colon empties in twenty-four to thirty-six hours and the barium is scattered through the left half of the colon or is all in the rectum. This residue is almost entirely removed by subsequent irrigation. Slight gain in weight; blood-pressure remains the same; has worked steadily for fifteen months as draftsman. (Appendicostomy still open twenty-seven months after operation, January, 1920.)

CASE IV.—Mrs. B. S., aged twenty-six years; married one year. Diagnosis: epilepsy, ptosis; colon stasis.

Father and mother well; three sisters nervous; two brothers and one sister well. For twelve years had constipation; daily laxatives; epigastric distress and gas; occasional headache; for nine years had epilepsy, usually nocturnal, one or two attacks a month; slight mental depression; memory poor; bromides for a year; weight six years ago 124 pounds, now 110 pounds.

Poorly developed and nourished; neurotic; slightly stupid; irregular teeth; tonsils slightly enlarged; heart and lungs normal; cecum palpable and slightly tender; gurgles on palpation; stomach contents after test breakfast nothing abnormal; urine normal. Roentgen-ray examination showed marked ptosis of the stomach (five inches); colon entirely below the crest of the ileum; stomach and small intestine emptied in approximately normal time; colon well filled throughout up to fifty hours.

Appendicostomy, September, 1918. Daily lavage for six months; attacks stopped for two months, then were just as frequent as before; some were milder; general condition improved somewhat; less depression and nervous symptoms; gain of five pounds; appendicostomy was allowed to close after six months.

NEUROBLASTOMA SYMPATHICUM: REPORT OF ONE CASE.<sup>1</sup>

BY P. C. GUNBY, M.D.,

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SINCE the publication, in 1910, of Wright's<sup>2</sup> article on neuroblastoma, the recognition of tumors of sympathetic nerve-cell origin has been more frequent, and several additional cases have been described. The case herein reported is an example of this type of tumor in which clinical diagnosis was confirmed by post-mortem examination.

Case 257376, a boy, aged thirteen years, came to the Mayo Clinic January 1, 1919, for the relief of failing vision, weakness and "small lumps" in the scalp. One other child in the family had "multiple necroses of the skull." The mother had had four miscarriages. The patient had had croup at four and pertussis at six; his tonsils and adenoids had been removed four years before. He was in the eighth grade at school. Six months before examination the parents had noticed small lumps in his scalp, pallor and loss of strength. The local physician examined the eye-grounds and reported choked disks; he prescribed potassium iodide in small doses. Loss of strength and vision had been progressive and the tumors in the scalp had doubled in size. For a month there had been intervals of pain in the knees and hips. There had been scarcely any headache and no vomiting. Sphincter control had always been normal. He had never suffered hemorrhage from the mucous surfaces nor any skin rashes, and there was no history of gastro-intestinal or genito-urinary disturbance.

The examination revealed a well-developed boy, moderately emaciated, whose skin was very pale, with a slight greenish tint. The entire forehead and vertex were nodular, with tumors varying in diameter from 2 cm. to 6 cm. Some of the nodules were rather soft, others quite hard. They were not movable and apparently were attached to the cranial bones. The site of the anterior fontanelle was sunken and the cranial sutures generally were separated. The superficial veins of the scalp were greatly dilated. Moderate bilateral exophthalmos was present in almost equal degree. The cervical glands on both sides were only slightly enlarged, but were very hard. Tenderness was extreme on firm pressure over the sternum and along the course of the ribs. A smooth liver edge was palpable on deep inspiration and a smooth mass was also felt in the left hypochondrium; this mass, which descended on inspiration, was suggestive of the spleen, although a

<sup>1</sup> Presented for publication, March 24, 1920.

<sup>2</sup> Neurocytoma or neuroblastoma, a kind of tumor not generally recognized, Jour. Exper. Med., 1916, xii, 556-561.

notched border was not distinct. Careful palpation of the left flank several times by different examiners gave no suggestion of a retroperitoneal mass. The right testicle was undescended.

The breath sounds were clear over both lungs. The heart-rate was rapid, and the pulmonic second sound was accentuated rather markedly. The rhythm was regular, but there was a blowing systolic murmur at the base of the heart, not transmitted.

Ophthalmological examination revealed bilateral choked disk of two diopters. A detailed neurological examination yielded negative results.

The urine contained nothing significant; Bence-Jones's protein was absent. The hemoglobin (Dare) was 30 per cent.; the erythrocytes were 1,580,000 and the leukocytes 6200; the differential blood count was normal and the blood-Wassermann reaction on both the patient and the father were negative.



FIG. 1.—Roentgenologic appearance of metastatic tumor in the skull bones.

In the roentgenogram of the skull there was evidence of a diffuse porosity suggesting the osteoclastic type of bone-malignancy (Fig. 1). Papules and some scarring about the body were noted. In view of this and the roentgenological finding, the familial history of miscarriages, some suggestive scarring about the uvula and fauces, and slight roughening of the tibiae, Dr. Stokes considered the possibility of hereditary syphilis. Because of the tumor in the left hypochondrium, the anemia, the cranial tumors, the exophthalmos and the roentgen-ray findings I had suggested a diagnosis of neuroblastoma sympathicum, probably primary in the left

adrenal. This condition, however, is too rare for positive diagnostic conviction, and antiluetic therapy was instituted.

For four days after the patient was admitted to the clinic the temperature ranged from 100° to 102° F., but then returned to normal, and remained so. The pulse-rate varied from 90 to 150. At intervals there was much pain in the knees and in the back. The child's condition remained essentially the same for two months; he then died.

The postmortem examination was conducted by Dr. W. W. Bissell, and the following pertinent lesions were named in the anatomic diagnosis:

"Large malignant hypernephroma (?); of the left adrenal; multiple extensive hypernephroma (?) metastases to the bones of the skull, the sternum, vertebræ, ribs and to the lateral lumbar and retro-aortic lymph nodes; very extensive tumor rarefaction and softening of the skull bones; very extensive tumor pressure molding of the brain; very marked bulging (pressure exophthalmos) of both eyes; marked bilateral disseminated hypostatic bronchopneumonia; moderate catarrhal tracheobronchitis; marked hyperplasia and hyperemia of the spleen; slight hyperplasia of the tracheobronchial lymph nodes."

Abstracts from the protocol are as follows:

"This is the body of a very well-developed, but very poorly nourished young white boy, apparently in the neighborhood of fourteen years of age. There are numerous nodules in the tissue of the scalp which, to the feel, are attached to the bone and vary in size from less than 1 cm. to 5 or 6 cm. in diameter. It is noteworthy that the head is considerably enlarged, being broadened in the temporal diameter. The root of the nose is greatly broadened. The distance between the pupils has the appearance of having been widened. There is no squint, but the eyes are protruding. In either upper lid, but more particularly in the left, there is a black-and-blue discoloration, as if this exophthalmos were, so to speak, 'acute.'

"In placing the body on the table perfectly straight, it is distinctly observed that the left flank is slightly more rounded than the right, the fulness being more marked just below the costal arch. No distinct mass, however, can be felt in the left flank. The skin of the body generally is quite pale. There is a very slight edema in the subcutaneous tissues about the ankles. The sternal end of the right clavicle is quite prominent and the skin over this particular area is somewhat tighter than the skin elsewhere on the body, for example, over the ribs.

"On opening the body through a midline, ventral incision, a considerably enlarged spleen presents beneath the costal arch; to the feel this is the spleen of hyperplasia. A larger mass beneath the spleen and pancreas fills the left upper abdominal quadrant.



It is fist-sized, of irregular shape and nodular, and is attached to or in close relation with the upper pole of the left kidney. This tumor mass is entirely retroperitoneal. It is a tumor of the left adrenal gland, and in no sense involves the kidney. Some of the nodules on its surface, particularly those of light pink color, are quite firm, while others of deep red color are slightly fluctuant. On surfaces made by sectioning the light salmon-pink nodules are of the consistency of brain tissue, while the deep red ones are gelatinous, easily destroyed by pressure and ooze blood freely. This tumor has originated from the left adrenal gland. It is directly continuous with it, and only a very small remnant of adrenal cortex remains intact, a small ear of the upper pole.

"The retroperitoneal and lateral lumbar lymph nodes are the seat of a neoplastic infiltration; an infiltration with tumor substance of the consistency and color of the adrenal tumor. In the lumbodorsal vertebral column there is a very extensive involvement of the bodies of the vertebræ together with their arches; an involvement entirely similar to that noted below in the skull.

"Just over the sternal end of the left clavicle, where the skin is somewhat tight, there is a small lymph node which is the seat of tumor metastasis. The ribs and sternum are the seat of many very early hemorrhagic tumor metastases, most of which have not yet broken through the medullary portion of the bone.

"The nodules in the scalp are tense, some of them slightly fluctuant; others more markedly so. On reflecting the scalp these nodules are found to be beneath the pericranium. They are very firmly attached to it, and it is with great difficulty that the scalp tissues are reflected without more or less destruction of these nodules. These tumors take origin in the medullary portion of the bone; the outer table of bone is honey-combed in such a way that numerous little prickles of bony material project from the skull. The larger tumor masses are formed from a conglomeration of many small nodules (Fig. 2). The entire calvarium is very flexible in any direction of pressure. On viewing it from the inside, many variable sized tumor masses, covered by dura, bulge inward toward the brain (Fig. 3). These are deep chocolate to light yellow in color. On opening some of these thicker tumor masses in the temporal regions they present areas of deep red hemorrhage; in other places the appearance suggests that of brain tissue, yellow to salmon-pink in color. In four places these extradural tumors have perforated the dura, but have remained slightly encapsulated, not involving the leptomeninges. The largest of the tumor masses from the inner surface of the skull measures 5 cm. by 4 cm. by 2.5 cm.

"Wherever the tumor has bulged into the cranial cavity there is a corresponding facet or depression in the brain itself. The brain is molded into an irregular, lobated organ (Fig. 4). In the right

temporoparietal region appears the largest molding, a cup measuring 4 cm. in diameter and 2 cm. in depth. In the base of the



FIG. 2.—Outer surface of the calvarium.

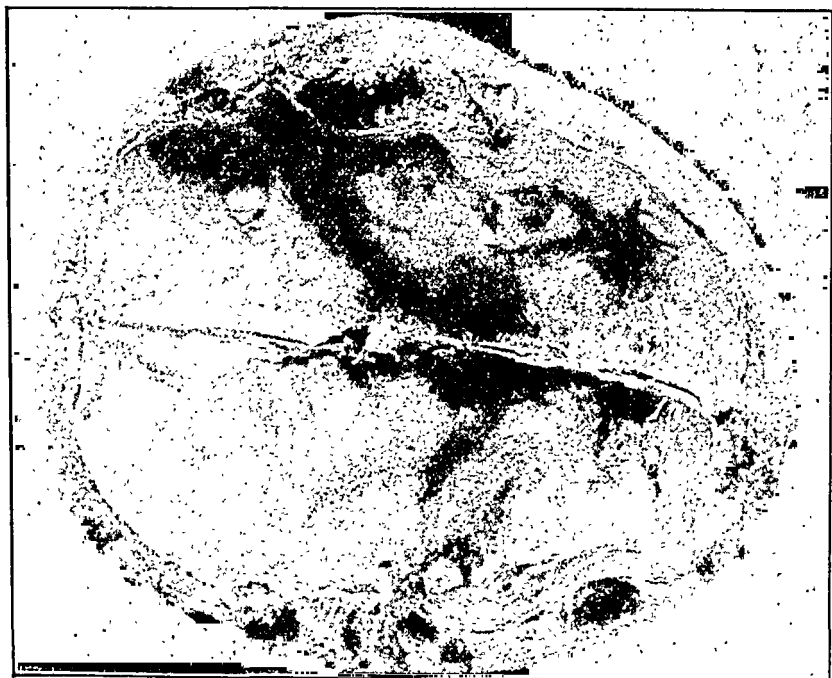


FIG. 3.—Inner surface of the calvarium.

skull there are only a few of these metastases, the largest arising in the right anterior fossa and bulging into the right orbit rather than into the cranial cavity.

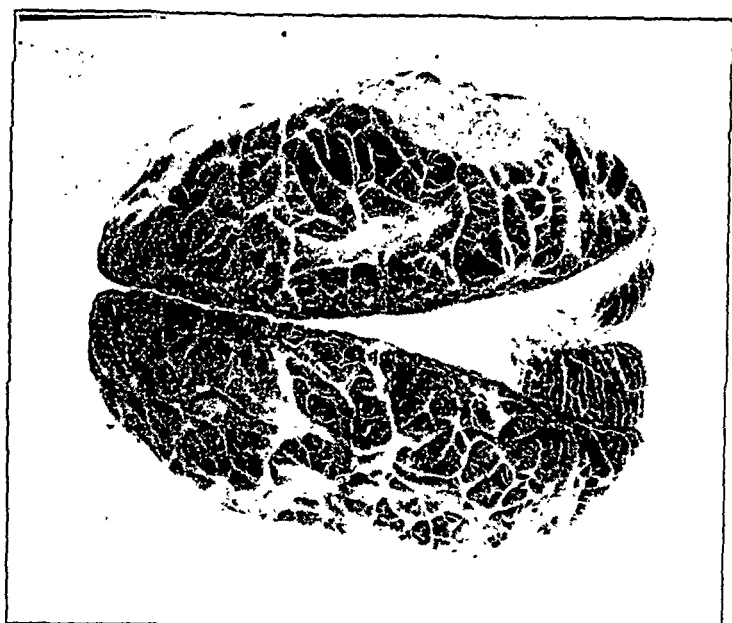


FIG. 4.—The superior aspect of the brain; marked pressure molding apparent.

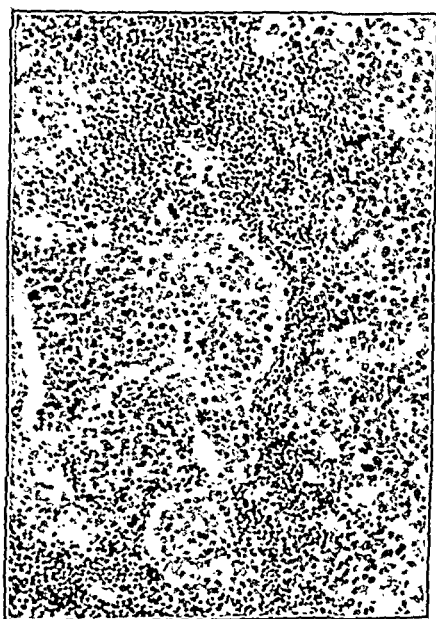


FIG. 5.—Metastatic tumor in a lymph node.  $\times 100$ .

“There are no metastases to be found in any of the parenchymatous organs—they are confined to the osseous and lymphatic tissues.”

In microscopic specimens of the adrenal tumor proper, as well as in those taken from blocks of the metastatic nodules (Fig. 5), none of the characteristics of hypernephroma were found. Areas



FIG. 6.—Great variation in the size and form of tumor cells; rosette in the center of the field.  $\times 500$ .

of recent hemorrhage occurred throughout. The tumor cells were arranged indiscriminately, rather closely packed in some places

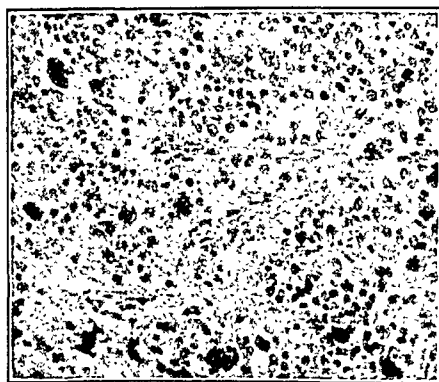


FIG. 7.—Two primitive ganglia in the field. Many tumor giant cells with one foreign body giant cell near the top of the field.

with very little connective-tissue stroma. In other areas a considerable amount of young fibrous tissue widely separated the aggregates of tumor cells. The tumor cells varied in size (Fig. 6),

the nuclei of the greater number approximated the size of a small lymphocyte; the predominant shape was oval. The chromatin was evenly spread through the nucleus and stained rather deeply. In the larger cell forms, which in places were twice the size of a small lymphocyte, the nuclear outline was very irregular; the chromatin in discrete granules and a well-marked nucleolus were present. These larger forms did not stain so deeply as the smaller ones. Rosette formation was present, but not uniformly throughout the tissue (Fig. 7). In a few places were bundles of very fine fibrils in association with clumps of tumor cells, presenting the appearance of primitive sympathetic ganglia (Fig. 6). There were many true tumor giant cells, with an occasional foreign body giant cell (Fig. 6); mitotic figures were numerous. A piece of tissue removed from the left adrenal contained a bit of normal cortex; the medulla, however, was entirely replaced by tumor tissue.

With these observations a diagnosis of neuroblastoma sympathicum was established. Grossly the striking similarity of this tissue to that of hypernephroma might lead to a mistaken gross diagnosis were it not for the extraordinary metastases to bone, particularly to bones of the skull.<sup>3</sup>

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## INFLUENZA IN THE TUBERCULOUS.

BY MAURICE FISHBERG, M.D.,

AND

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DURING the recent pandemic of influenza we have been struck by several paradoxical phenomena in the etiology and clinical course of tuberculosis of the lung. There is ample and reliable evidence that nearly everyone living in a modern city has been infected with tubercle bacilli at some period of his life, usually before he has reached adolescence. It appears that this infection is effective in producing pathological changes in the lung and pleura, but that these morbid changes remain latent in the vast majority of cases. Attempts to explain the reason why in some persons tubercle bacilli produce disease and perhaps death, while in others they remain within the body merely as harmless invaders, have suggested the importance of a "predisposition" which varies with the individual. Among the factors which reduce the resisting powers or enhance

<sup>3</sup> Dr. J. H. Wright, of the Harvard Medical School, also examined specimens from the tumor and verified the diagnosis.

predisposition, influenza or the microörganism responsible for it has been considered as one of the most effective. Similarly the undulating course of chronic pulmonary tuberculosis has been explained as due mainly to mixed infections, especially to streptococci and to the Pfeiffer bacillus, which often are found in abundance in the sputum of tuberculous patients. It has been claimed that patients who are so fortunate as to escape superinfection with the secondary invaders do well, while those who are thus infected run a more or less stormy course, ending finally in death.

In a previous communication on this subject<sup>1</sup> it was shown that during the epidemic of 1918-19 influenza could be exonerated from the charge of playing an important role in the etiology of tuberculosis and in affecting its clinical course. Nowhere has there been observed an increase in the morbidity and mortality from tuberculosis soon after the subsidence of the epidemic. Clinical observation revealed the astonishing fact that tuberculous patients stood the acute epidemic disease quite well; it appeared that the proportion of fatal cases was not greater but apparently even smaller than among the non-tuberculous. This fact has so far been confirmed by most writers on this subject, who have based their assertions on observations of large numbers of cases. Thus F. H. Gerwiener<sup>2</sup> had similar experiences in a Hungarian military sanatorium of 2400 beds. The epidemic was raging in the city and in the suburban villages, and no precautions were taken to keep the plague out of the institution or to isolate the patients. Yet very few cases occurred among the tuberculous patients in the sanatorium. It is, however, noteworthy that among the healthy personnel of the sanatorium, the physicians, nurses, orderlies, numerous and severe cases of influenza were observed. Similarly, Bochall<sup>3</sup> observed that tuberculosis created a certain degree of immunity against influenza, and that, when tuberculous patients are affected, the prognosis is much better than in non-tuberculous individuals. Wurtzen,<sup>4</sup> comparing the morbidity and mortality from influenzal pneumonia among tuberculous patients with that in previously healthy individuals, found that the chances of contracting pneumonia are about the same in both groups. However, while 36 per cent. of previously healthy soldiers succumbed to influenzal pneumonia, 83 per cent. of those who were tuberculous died. In France, Weil reports from the services of Léon Bernard and Rist, at the Laennec Hospital, that two wards filled with 50 civil tuberculous patients were completely spared during the influenza epidemic; that in four wards with 105 military patients only 3 cases of in-

<sup>1</sup> Fishberg, M.: Influenza and Tuberculosis, *Am. Rev. Tuberc.*, 1919, iii, 532.

<sup>2</sup> Die pandemische Grippe in ihren Beziehungen und Folgeerscheinungen zur Lungentuberkulose, *Beit. z. Klin. d. Tuberkulose*, 1919, xlii, 33.

<sup>3</sup> München. med. Wchnsch., 1919, lxvi, No. 12.

<sup>4</sup> Ugeskr. f. Laeger, 1919, lxxxi, 673.

fluenza occurred; and in the female wards, with 50 beds, only 9 cases of influenza appeared.<sup>5</sup> In the Boucicaut Hospital influenza invaded every ward except the tuberculosis ward.<sup>6</sup> In two sanatoriums Albert Bezançon and Guniard observed only 8 cases, or 1.7 per cent., among 448 tuberculous patients, in contrast to 32 cases, or 28 per cent., among the 120 healthy employees. Similar observations have been made by Debré and Jaquet.<sup>7</sup>

Available evidence thus shows that the tuberculous are no more predisposed to infection with the virus of influenza than are the non-tuberculous; indeed, it would seem that when infected they stand the disease better than others. This is not in agreement with certain theoretical observations which have accumulated in the study of the phenomena of immunity. Influenza, like any other infectious disease, should predispose the body to tuberculous infection or favor the extension of existing tuberculous processes; latent disease should be reactivated and active disease should be stirred up to acute or subacute progression. Anergy, in the sense given to it by von Pirquet, is characteristic of most of the infectious diseases. This holds true in the case of vaccine virus, which produces over 90 per cent. of allergic reactions in normal individuals, and shows anergy in from 50 to 90 per cent. of persons suffering from measles, scarlet fever and the like.

Anergic reactions have been found in patients suffering from influenza by many who have studied the subject. Bloomfield and Mateer,<sup>8</sup> observing that patients with influenza have a low leukocyte count, investigated whether any of the reactive processes were in abeyance. They found that the tuberculin skin test proved negative in all cases during the febrile stage. This was true in both mild and severe cases. During convalescence reactivity returned in 89.4 per cent. of the cases, which corresponds to the incidence in a group of normal individuals of the same age. The return to maximum reactivity, as shown by successive tests, was gradual in most instances. In two patients a positive cutaneous reaction was not obtained during the period of observation even after the temperature had been normal for from six to eight days. Similar observations have been reported in Europe. Debré<sup>9</sup> found that 72 per cent. of patients suffering from influenza and its complications failed to give allergic reaction after inoculation with vaccine virus. Lereboullet found that in the vast majority of persons who have recently passed through an attack of influenza the cutaneous tuberculin reaction was negative or feeble.<sup>10</sup> Berliner<sup>11</sup> reports 19 per cent.

<sup>5</sup> Weil: Contribution à l'étude de la grippe chez les tuberculeux pulmonaires, Thèse de Paris, 1919.

<sup>6</sup> Britcaire: Le reveil de la tuberculose par la grippe, Thèse de Paris, 1918-1919.

<sup>7</sup> Grippe et Tuberculose, Paris Médical, 1920, x, 24.

<sup>8</sup> Johns Hopkins Bull., 1919, xxx, 238.

<sup>9</sup> L'anergie dans la grippe. Soc. de biologie, October 26, 1918.

<sup>10</sup> Lereboullet: Paris Médical, 1918, viii, 389.

<sup>11</sup> Deutsch., med. Wehnschr., 1919, No. 9.

positive tuberculin reactions in individuals suffering from influenza as against 85 per cent. in normal people. Schiffer<sup>12</sup> noted the same phenomenon in children.

It is because of these studies that the observations reported below are of significance. During the epidemic of influenza of 1918 the patients in the tuberculosis pavilion of the Montefiore Hospital suffered but little from the acute complicating disease, which ran a mild course, as a rule; only a few contracted bronchopneumonia and but two died. In private practice similar observations were made. Others, however, report that influenzal pneumonia, when attacking tuberculous patients, is more likely to prove fatal than in previously healthy individuals. Thus in papers recently published by Permin,<sup>13</sup> Bricaire<sup>14</sup> and others it is shown that influenza is likely to stir into activity dormant tuberculous foci and to prove fatal when attacking phthisical patients. We have observed some differences both in the clinical course and in the mortality of influenza in tuberculous patients between the epidemic that occurred in the first two months of this year and the one of 1918. During the former epidemic the incidence of influenzal pneumonia was rather low while this year it was high. Coincident with the high morbidity rate of pneumonia the relative number of fatal cases has increased. Whether this is to be explained by the hypothesis that there are several strains of influenza virus, as has been suggested by some authors,<sup>15</sup> is a subject worthy of study. However, the fact that influenza is accompanied by anergy, coupled with the leukopenia usually observed in this disease, would lead us to expect that in most cases the effect on the existing tuberculous process would prove disastrous. It is with a view of determining this point that the details of the epidemic in our hospital are herewith reported.

During the recent influenza epidemic the disease appeared in the tuberculosis division of the Montefiore Hospital. The tuberculosis pavilion has two stories divided into four ward units (I and II on the ground floor, III and IV on the second floor), accommodating altogether 136 patients. Each unit consists of a ward of 14 beds and 10 rooms each containing 2 beds. A study of the epidemiology of the outbreak reveals no very clear avenue of extension. The first case occurred in a nurse on Ward IV on January 10, 1920. On January 14 a patient orderly on Ward II became ill. He presumably was not exposed to infection from the nurse on Ward IV. On January 16, 1 case occurred on Ward II, 1 on Ward I and 2 on Ward IV. During the next six days there was a rapid spread of cases on Wards III and IV, 13 patients being stricken, while only 1 patient on Ward II became ill. At the same time three more nurses on Ward IV contracted the disease. From January 23 to February

<sup>12</sup> *Monatsschrift f. Kinderheilk.*, 1918, xv, 189.

<sup>13</sup> *Ugeskr. f. Laeger*, 1918, lxxx, 1739.

<sup>14</sup> *Stallybrass, C. O.: The Periodicity of Influenza, Lancet*, 1920, i, 372.

<sup>15</sup> *Loc. cit.*



14 only 9 new cases appeared, occurring singly, and distributed among all of the wards. In a number of instances when one patient in a small room became ill, his or her companion in the adjoining bed sickened several days later. Four cases occurred within three days of one another in the ward in Unit IV, a fifth case appearing two weeks later. The severe and fatal cases all had their onset between January 16 and January 24. The preceding and subsequent cases were relatively mild. Altogether there were 28 cases among the patients and 4 among the nurses. From January 10 to February 14, 1920, the average census of the tuberculosis service was 127 patients. During the same period six nurses were on duty. Thus while only 22 per cent. of the patients contracted influenza the morbidity among the nurses was 66 $\frac{2}{3}$  per cent.

Apparently the disease was introduced into Ward IV by the nurse who was first taken ill. It appeared independently in Wards I and II. It then spread rapidly and was favored in its extension by close contact, such as that of two individuals in the same room. It is noteworthy that it did not single out any particular type of patient, for both those with active and inactive tuberculosis, both the old and the young were infected.

This year the epidemic exacted a heavy mortality, 9 of the 28 cases, that is almost a third of them, succumbing. All of the patients who died had advanced pulmonary lesions, but many of those who recovered had quite as extensive tubercular involvement. A young girl with a congenital stenosis of the pulmonary artery, marked cyanosis, and advanced tuberculosis was among the fatal cases. The clinical course of the influenza resembled that seen in the non-tubercular. Six of the patients ran a mild course. The onset was acute, with sore-throat, general body pains and sudden rise in temperature. In a number of cases the day before the striking febrile reaction the temperature was about 1° higher than it had been. On physical examination the patient appeared prostrated, the pulse was rapid and weak and the throat red and dry. The eyes were not injected. No new physical signs appeared, the temperature remained irregularly elevated for from four to five days and dropped by crisis or rapid lysis. The attack left the patient weak, but otherwise did not appear to affect him much, save in one man, who two weeks after the subsidence of the attack still ran an irregular fever up to 100.6°, whereas before the onset of the influenza his temperature had been practically normal. Neither he nor any of the other patients showed any extension of their tubercular lesions as manifested by physical signs. The following protocol illustrates one of these mild cases.

No. 40569. N. B., aged thirty-two years, male.

Duration of tuberculosis, five years. Lesion: infiltration of both upper lobes. Sputum showed no tubercle bacilli. Inactive.

January 21, 1920. Sore-throat; general body pains; marked prostration. Temperature, 103°.

January 24. Temperature and symptoms continued until today, when the fever dropped by crisis. No new lung signs during the febrile period.

January 28. Patient feels well. Temperature normal. Physical signs in chest as before influenza.

Twenty-two of the cases were complicated with a bronchopneumonia. The onset of the bronchopneumonia was gradual; very few of the patients had a real chill. It was suggested by the persistence of fever for more than four days, by increasing prostration and by rapid breathing and cyanosis. Not infrequently days elapsed before physical signs became manifest. This, of course, is seen in the non-tubercular as well, but extensive tubercular infiltration of the lungs makes the recognition of new physical signs more difficult. The physical signs, when they appeared, were usually at one or both

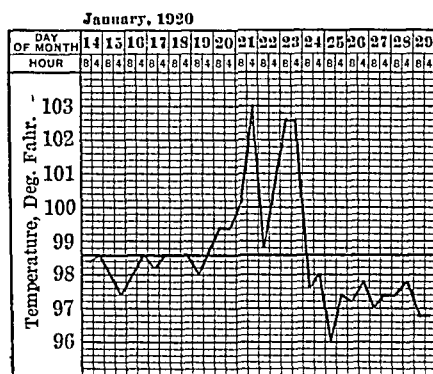
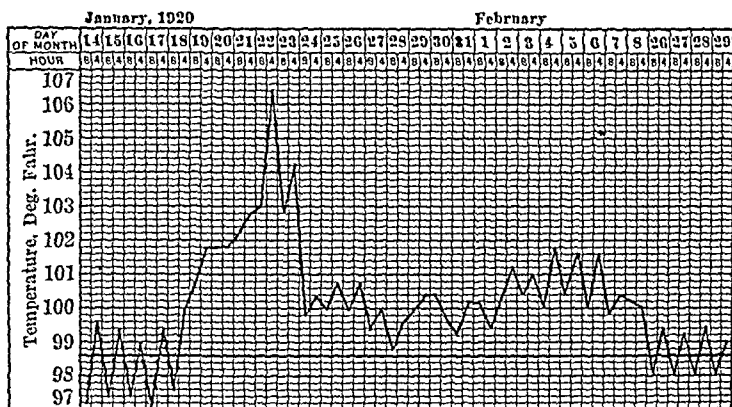


CHART I.—Uncomplicated influenza in a case of inactive tuberculosis.

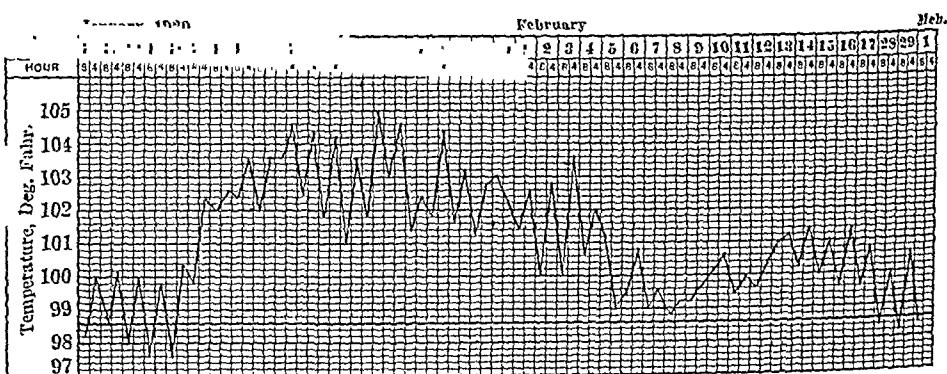
bases, and consisted of diminished breath sounds, moist rales, dulness and only occasionally bronchial breathing. Only a few patients had definite signs of upper lobe involvement, but undoubtedly the old tubercular lesion rendered their appreciation impossible in many instances. In 4 cases without new lung signs bronchopneumonia was diagnosed because of the persistent fever, great prostration and dyspnea.

The course of the pneumonia did not differ from the usual one, the previous tubercular fever having no influence on the temperature curve. This is illustrated by Charts II and III. Bloody sputum was of frequent occurrence, but other hemorrhages were not seen. The duration of the febrile stage of the bronchopneumonia varied greatly. One patient died within two days; the longest course was five weeks and ended in recovery. The most frequent duration was from one to two weeks. The physical signs often persisted for days after the subsidence of the fever. The fatal cases

In those patients who recovered, several days elapsed after the subsidence of the bronchopneumonia before the typical tubercular temperature curve, with its afternoon rise, became manifest.



For instance, in one case for three days after the bronchopneumonia had passed the temperature stayed below  $100^{\circ}$  without an afternoon rise. Then gradually the afternoon elevation appeared, and in about ten days after the defervescence of the intercurrent fever the original temperature curve of the patient was reestablished. This was observed a number of times, and is illustrated by Chart III.



In most cases the course of the tuberculosis was apparently uninfluenced by the influenza, except in so far as the general condition of the patient was impaired. Of course, all of the patients who survived a severe bronchopneumonia were very weak and shaky for some time and lost weight, but, so far as could be judged

from the fever and the physical signs, the tuberculosis had remained unaltered. In three cases, however, the temperature curve, which had been practically normal, now shows a regular afternoon rise to about  $101^{\circ}$  (Chart IV). In only one of these patients are there physical signs indicating extension of the lesion. In this instance

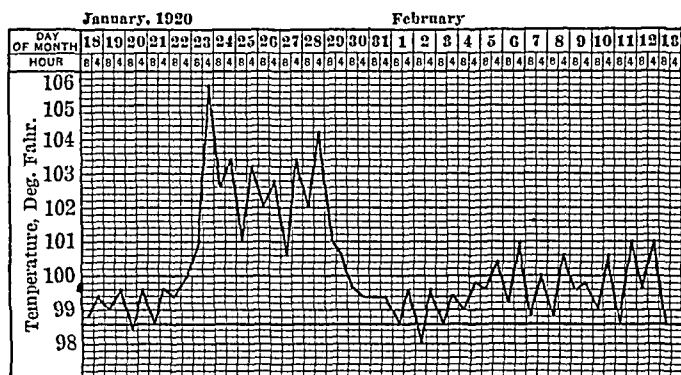


CHART IV.—Previously a febrile case becomes febrile after influenza.

persistent crepitant rales have appeared in the right infraclavicular fossa, which were never heard before. The following cases are typical of those with a fatal termination:

No. 38263. M. D., female, aged eighteen years.

Duration of tuberculosis, three years. Extensive bilateral infiltration and cavitation. Tuberculous enteritis. Active case. Sputum positive.

January 26, 1920. Temperature more elevated than usual.

January 19. Temperature continues; headache; sore-throat; prostration.

January 21. No change in physical signs; sputum blood-streaked.

January 24. Coughed up much blood. Moist rales at right base posteriorly. General condition fairly good.

January 25. Death at 5.45 A.M.

No. 02607. S. L., female, aged twenty-three years.

Duration of tuberculosis, four years. Infiltration and cavitation of left lung and right apex. Tuberculosis of left ankle. Moderately active. Sputum positive.

January 20, 1920. Severe headache; body aches; temperature,  $102^{\circ}$ .

January 26. Temperature has remained up. Consolidation of lower half of right lung. Finger tips cyanotic; dyspnea. Extreme retching; vomitus bloody; sputum bloody.

January 27. Marked cyanosis. Lungs full of bubbling rales. Death at 10 A.M.

In some cases with severe symptoms of influenza the final outcome was favorable. The following may serve as an illustration:

No. 35778. P. B., female, aged twenty years.

Duration of tuberculosis four and a half years. Bilateral infiltration and cavitation. Active. Sputum positive.

January 16, 1920. Pain in chest; temperature a little elevated.

January 17. Sore-throat; chills; general aches; temperature; 102.4°.

February 1. Temperature has continued at about 103°. Subcrepitant rales at both bases. Great prostration; pulse weak; respirations rapid; sputum bloody. Sputum culture yielded influenza bacilli.

February 5. Temperature has dropped to 99° by lysis.

February 9. Marked weakness; general condition decidedly worse than before influenza. Rales at bases persist.

February 9. Bases of lungs clear; temperature as before influenza. No extension of tubercular lesion. Patient is still weak and has lost in weight.

In 5 out of 9 cases in which sputum cultures were made the influenza bacillus was recovered.

SUMMARY. 1. In an outbreak of influenza in the tuberculosis pavilion of the Montefiore Hospital during January and February, 1920, 28 out of 127 patients were affected. The proportion seems to be about the same as might be expected among non-tuberculous individuals.

2. The clinical form of tuberculosis and the stage of the disease had no influence on the liability of the patients to contract influenza.

3. Of the 28 patients who contracted influenza 9 died, which is a higher ratio of mortality than is generally observed. Of the 28 patients with influenza 22 developed bronchopneumonia, again a rate much higher than usually seen.

4. It seems that the liability to complicating bronchopneumonia varies with the epidemic. During the epidemic of 1918 a lesser proportion of our patients developed this complication and the mortality was lower.

5. The clinical course of the influenza resembled that seen in the non-tuberculous. The liability to develop complicating bronchopneumonia bears no relation to the stage, clinical form or acuteness of the tuberculous process in the lung and pleura.

6. In nearly all of the patients who recovered the complicating disease had no appreciable influence on the tuberculous lung lesion so far as could be ascertained by physical exploration of the chest or on the subsequent course of the disease.

7. We cannot say that the anergic state brought about by influenza has had an influence on the incidence, course and termination of this disease in the tuberculous.

## A CHEMICAL STUDY OF BLOOD CHANGES FOLLOWING ROENTGEN-RAY TREATMENT OF LEUKEMIA.

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AND

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DURING the twenty years which have elapsed since the introduction of the roentgen-ray treatment of leukemia, a considerable number of investigations have been published dealing with the urinary changes produced by splenic radiation.<sup>1</sup>

As yet, however, practically no data are available regarding the chemical changes brought about in the blood by this method of treatment. In this paper we have collected the results obtained on four patients who were treated by one of us at regular intervals for the relief of leukemia. While the series is numerically smaller than we had hoped to obtain, it has seemed best, in view of circumstances which prevent the continuation of the work for an indefinite period, to publish the data so far collected.

In the main the following routine was observed with all the cases studied: Roentgen-ray exposures of the spleen were made at stated intervals as described in detail below; just before entering the treatment room a white count was made and a sample of blood taken for chemical analysis; the determinations of basal metabolism were made as often as possible on the morning of the day on which treatment was given; occasionally it was necessary, however, on account of press of work in the respiration laboratory, to make this observation in the interval between treatments.

The blood analyses were made by the methods of Folin and Wu.<sup>2</sup>

The basal metabolism determinations were made in Dr. J. H. Means's laboratory by Miss Margaret N. Woodwell. We are indebted to Dr. Means for the following description of the technic used:

"The patient's basal oxygen consumption was found with the Benedict universal respiration apparatus and the basal calories calculated for an assumed respiratory quotient of 0.79. The body surface was determined by the DuBois height-weight chart and the basal metabolism in terms of calories per square meter per hour expressed as a percentile deviation from the approximate normal

<sup>1</sup> Knudson, A., and Erdos, T.: Boston Med. and Surg. Jour., 1917, clxxvi, 503.

<sup>2</sup> Jour. Biol. Chem., 1919, xxxviii, 81.

standard. The standards used were those of the Russell Sage Institute."<sup>3</sup>

Each case was treated in practically the same manner. The skin of the left side of the abdomen, the left flank and the left back overlying the spleen were divided into squares measuring  $4\frac{1}{2}$  inches on a side. These squares were marked off with the aid of red ink and a small brush. The term "spleen area" as used on the charts refers to one of these squares. At each séance a fixed dose was given over 1, 2, 3 or 4 of these areas, depending upon how the patient reacted to the first treatment. Penetrating rays were used and the dose was as large as could be safely given without producing an erythema of the skin. A broad focus Coolidge tube energized by a Snook interrupterless transformer was placed so that the target skin distance measured eight inches, and each area was given 40 ma. minutes with the tube backing up an 8-inch parallel spark gap;  $3\frac{1}{2}$  mm. of aluminum and one thickness of sole leather were used as filters, and each square was surrounded with tinfoil shields during radiation. It has been noted that a severe reaction may follow radiation of the entire spleen at one seance, and consequently all of the areas used at one time were confined to one-half of the organ. As a rule the first treatment was given over the upper half of the spleen and the second over the lower half anteriorly, the third over the upper half and the fourth over the lower half posteriorly, each treatment consisting of three or four areas. About two days elapsed between each treatment. After a rest of one or two weeks the same series was repeated if necessary.

The data set down in this paper are taken for the most part from work done in the various laboratories of the hospital, and it is not our purpose to discuss leukemia from a clinical point of view. However, the following brief abstracts of clinical records give the outstanding symptoms and some of the important findings used in making the diagnoses in the four cases cited.

#### CASE I.—*Myelogenous leukemia.*

A white man, aged thirty-three years, entered the Massachusetts General Hospital November 10, 1919, complaining of headaches, weakness and feverish attacks. He had never been ill except for an attack of generalized rheumatism two years before admission which had kept him in bed sixteen days with swollen and painful joints.

Eighteen months previous to entering the hospital he had had an acute attack of pain in the left upper quadrant of the abdomen, referred to the left shoulder, which had lasted five days. This pain was relieved by lying on the left side. At the same time he had discovered that his abdomen was swollen and had begun to suffer from dizziness, edema of the legs and dyspnea. These symptoms

<sup>3</sup> Aub, J. C., and DuBois, E. F.: Arch. Int. Med., 1917, xix, 823.

had grown gradually worse. During the previous eight months he had had severe headaches, accompanied by slight deafness, nocturia and nose-bleeds. He had also felt feverish at intervals and perspired freely. There had been no diarrhea.

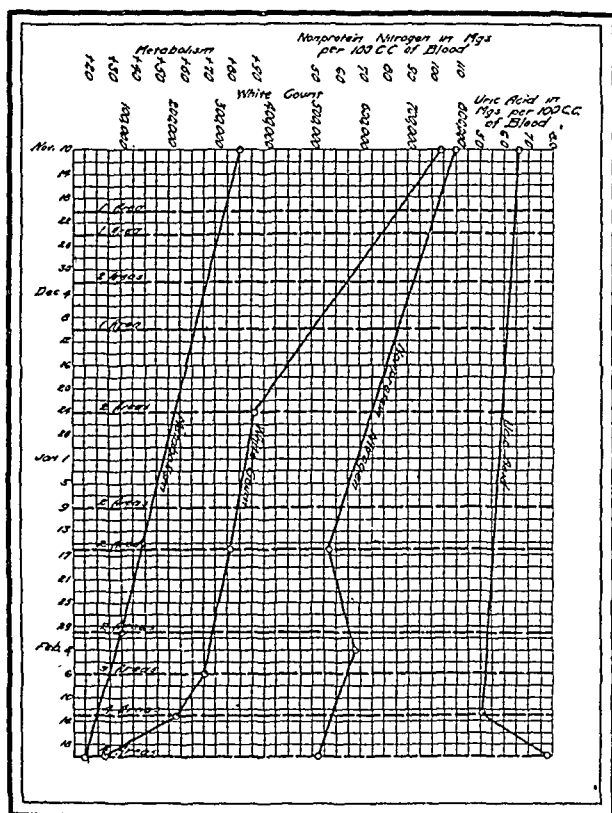


FIG. 1

TABLE I.—OBSERVATIONS ON BLOOD OF CASE I.

Date.	White cells.	Non-protein nitrogen, mg. per 100 c.c. of blood.	Creatinin, mg. per 100 c.c. of blood.	Uric acid, mg. per 100 c.c. of blood.	Remarks.
1919:					
Nov. 10	752,000	110.0	...	6.6	Before first treatment.
Dec. 24	376,000	86.0	1.5	...	Spleen slightly smaller; patient feels better.
1920:					
Jan. 16	326,000	57.0	...	...	Subjective symptoms much relieved; little change in spleen.
Feb. 20	65,000	54.0	...	7.6	Continued improvement.
Mar. 26	...	43.0	...	...	Patient relieved of most of his symptoms; color much improved; spleen now extends about a hand's breadth below the costal margin.



The patient was a well-developed and well-nourished man. There were small follicular patches on the tonsils. No abnormal signs were detected in the chest. The liver edge was felt 8 cm. below the costal margin. The spleen was resting in the pelvis and its inner edge could be palpated in the midline of the abdomen. At admission the red blood count was 2,484,000, the hemoglobin 50 per cent. (Sahli) and the white blood count 752,000. The differential count showed 69 per cent. polymorphonuclear cells, 1.5 per cent. lymphocytes, 0.5 per cent. large mononuclear cells and 29 per cent. of cells of the myelocytic series. A Wassermann test of the blood was negative. The specific gravity of the urine varied between 0.014 and 1.027 in seven twenty-four-hour specimens and the slightest possible trace of albumin was found in three. Red blood cells were found in one specimen and white blood cells in two. Amorphous urates were almost constantly present in the urine. Blood-pressure, 125/85.

CASE II.—*Myelogenous leukemia.*

A white woman, aged thirty-six years, entered the Massachusetts General Hospital February 4, 1920, complaining of headaches, vomiting and weakness. She had always been well until the present illness, except for two attacks of tonsillitis occurring nine years previous to admission.

About one year before entering the hospital she noticed a pain in her left side, which had been worse on lying down. A physician called in at that time had told her that she had an enlarged spleen. One month later she had begun to have occipital and frontal headaches in the morning, relieved by vomiting. These headaches had been accompanied by queer noises in the head. The symptoms had become much worse, and at admission she suffered from dyspnea on exertion, weakness and frequent vomiting. She had had several attacks of diarrhea lasting a week at a time, characterized by eight or nine bowel movements daily, containing blood and mucus. She had lost fourteen pounds in weight during the past year.

The patient was a fairly well-developed and well-nourished woman, showing general muscular weakness. The heart was not enlarged. The pulmonic second sound was louder than the aortic second sound and a systolic murmur was heard all over the precordia, loudest at the base. The heart sounds were regular, rapid and of good quality. No thrill was detected. The liver edge was felt 5 cm. below the costal margin. The mesial edge of the spleen was palpable in the midline of the abdomen and the lower pole extended down to the anterior superior spine of the ilium. There was slight edema of the ankles. The eye consultant stated that the outlines of the nerve heads were indistinguishable, that the retinal vessels were pale and enlarged and that the retina showed hemorrhages and degenerative areas. His diagnosis was "neuroretinitis."

At the time of admission the red count was 2,448,000, the hemoglobin 45 per cent. (Sahli) and the white blood count 856,000. The differential count showed 35 per cent. polymorphonuclear cells,

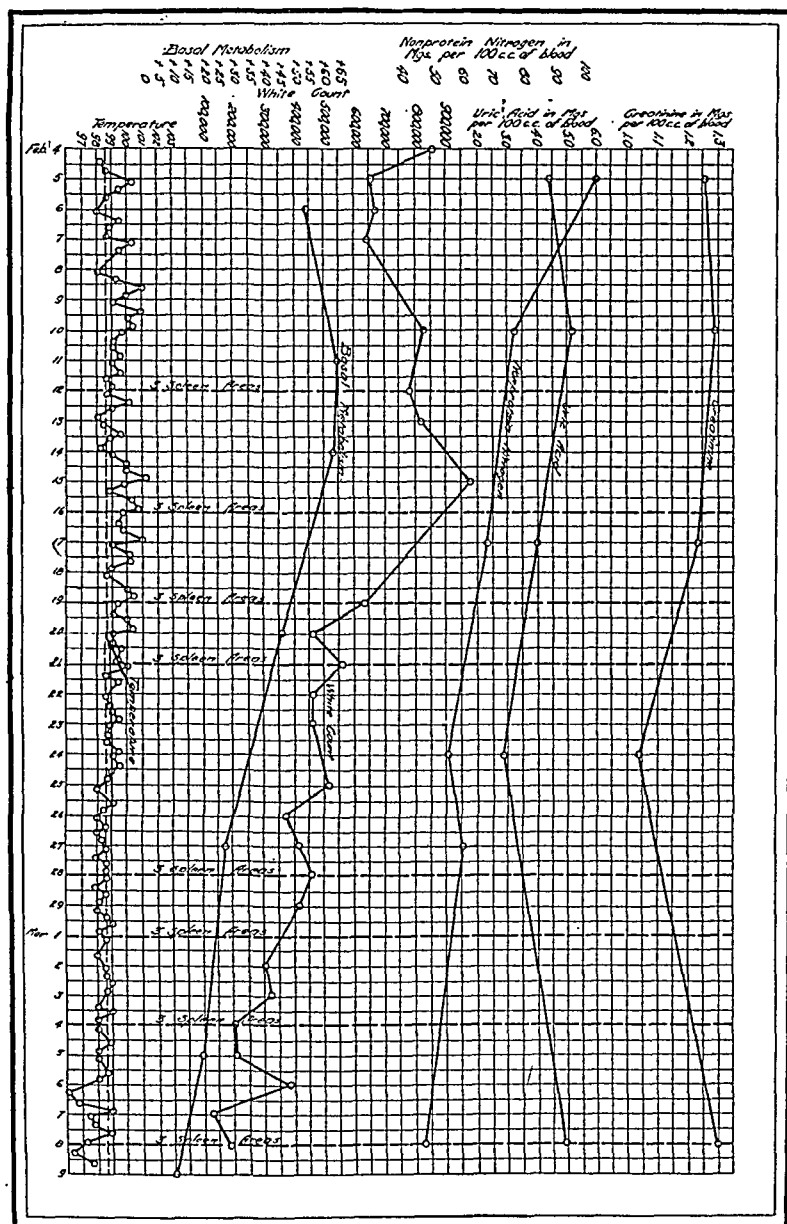


FIG. 2

2 per cent. lymphocytes, 2 per cent. eosinophiles, 3 per cent. basophiles, 10 per cent. neutrophilic myelocytes, 11 per cent. basophilic myelocytes, 4 per cent. eosinophilic myelocytes and 33 per cent. premyelocytes. Three normoblasts were seen in the smear. The

red cells showed aniso- and poikilocytosis and some achromia. The platelets were diminished. The Wassermann test was negative. The specific gravity of the urine varied between 1.009 and 1.030 in six twenty-four-hour specimens. A trace of albumin was found at one examination, a very slight trace at two and a slightest possible trace at one. The sediments showed occasional white cells, many amorphous urates and a rare hyaline cast. Blood-pressure, 120/80.

TABLE II.—OBSERVATIONS ON BLOOD OF CASE II.

Date.	White cells.	Non-protein nitrogen, mg. per 100 c.c. of blood.	Creatinin, mg. per 100 c.c. of blood.	Uric acid, mg. per 100 c.c. of blood.	Remarks.
1920:					
Feb. 5	658,000	105	1.26	4.45	Before first treatment.
Feb. 10	830,000	78	1.29	5.20	No improvement in subjective symptoms; severe diarrhea continues.
Feb. 17	...	68	1.20	4.0	Feels somewhat better.
Feb. 23	462,000	...	...	...	Gastro-intestinal symptoms have disappeared; feels definitely improved.
Feb. 24	...	56	1.04	3.0	
Mar. 5	216,000	53	1.32	4.0	Spleen is much reduced in size; patient relieved of all symptoms.

### CASE III.—*Myelogenous leukemia.*

A white man, aged, thirty-three years, entered the Massachusetts General Hospital February 19, 1920, complaining of weakness, dyspnea and afternoon chills. He had contracted gonorrhea, eleven years and again four years previously. He had been operated on for appendicitis eight years prior to admission. He had had attacks of tonsillitis every winter.

Four months before entering the hospital he had begun to feel tired and short of breath after slight exertion. He also had had mild frontal headaches, not relieved by laxatives. Two months later he had begun to have chills in the afternoon, followed by feverish attacks and severe night-sweats. One month later he had called in a physician because he had had a head cold and been told that he had an enlarged spleen. He had had no diarrhea, but had lost some weight.

The patient was a well-developed and well-nourished man. No abnormal signs were made out in the chest. The liver edge was not palpable and the dulness was within normal limits. The right border of the spleen was palpable well over on the right side of the abdomen and the lower pole was even with the anterior superior spine of the ilium. The red count was 3,284,000, the hemoglobin 70 per cent. (Talquist) and the smear showed 47 per cent. poly-

morphonuclear cells, 6 per cent. eosinophiles, 14 per cent. basophiles, 3 per cent. lymphocytes and 30 per cent. of cells of the myelocytic series. The white count was 360,000. The Wassermann test of the blood was negative. One twenty-four-hour specimen of urine had a specific gravity of 1.010 and the test for albumin was negative. The sediment contained a rare white blood cell.

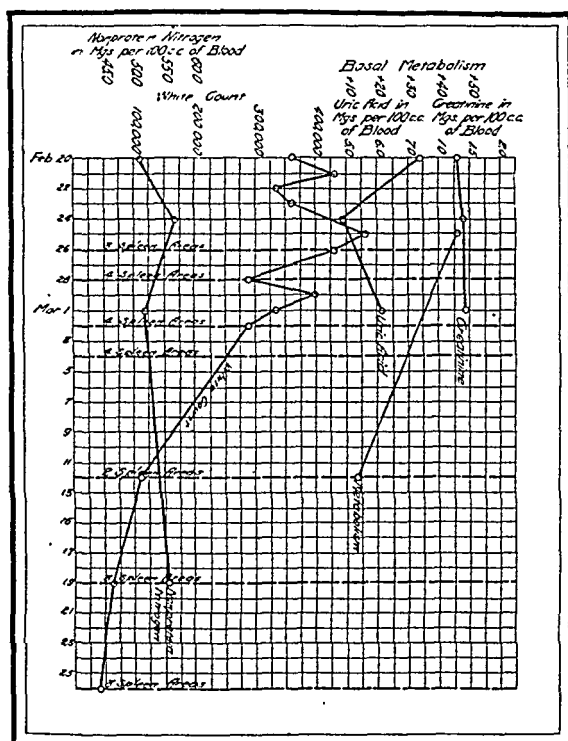


FIG. 3

TABLE III.—OBSERVATIONS ON BLOOD OF CASE III.

Date.	White cells.	Non-protein nitrogen, mg. per 100 c.c. of blood.	Creatinin, mg. per 100 c.c. of blood.	Uric acid, mg. per 100 c.c. of blood.	Remarks.
1920:					
Feb. 20	360,000	51.0	1.29	7.4	Before first treatment.
Feb. 24	364,000	56.6	1.32	4.9	Has felt well since entering hospital.
Mar. 1	336,000	52.0	1.46	6.2	
Mar. 19	60,000	55.0	...	...	Marked decrease in size of spleen.
Mar. 26	...	45.0	...	...	Patient continues to feel well.

#### CASE IV.—*Myelogenous leukemia.*

A white woman, aged twenty-seven years, entered the Massachusetts General Hospital December 31, 1919, complaining of

dizziness, headache and pain in the back. She had had attacks of "inflammatory rheumatism" seventeen, eleven, seven and five years and tonsillitis six years and one year prior to admission. She had had a gall-stone and appendix operation three years before entry and an attack of typhoid fever one year later; also an operation for pelvic abscess during the following year.

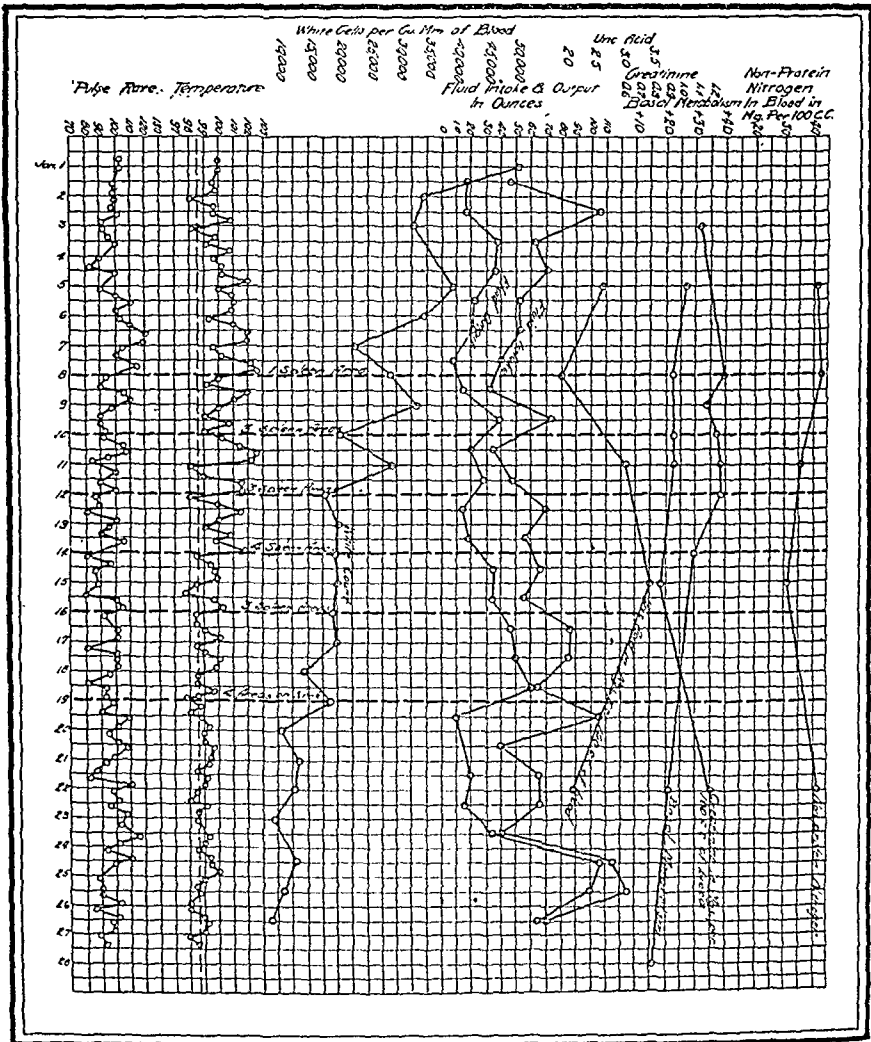


FIG. 4

Six or seven weeks before entering the hospital she had begun to have dizzy spells and generalized headaches, associated with dragging lumbosacral pain. This pain had been relieved by lying down. She had vomited when the pain was very severe. The night before coming to the hospital she had had a night-sweat. There had never been any diarrhea.

The patient was a well-developed and well-nourished woman. There were no abnormal lung signs, but the heart was enlarged and auscultation at the mitral area revealed both a presystolic and a systolic murmur. The pulmonic second sound was accentuated and greater than the aortic second sound. There was a short presystolic thrill felt in the sitting position. The liver edge was felt 4 cm. below the costal margin. The right border of the spleen was palpable in the midline of the abdomen and the lower pole extended down to the level of the anterior-superior spine of the ilium. The red count was 3,320,000, the white count 51,600 and the hemoglobin 70 per cent. (Sahli). The blood smear showed 43 per cent. polymorphonuclear cells, 6 per cent. lymphocytes, 9 per cent. large mononuclear cells, 2 per cent. basophiles, 10 per cent. basophilic myelocytes, 11 per cent. premyelocytes, 10 per cent. myeloblasts and 7 per cent. myelocytes. The Wassermann test of the blood was negative. The specific gravity of the urine varied between 1.012 and 1.018 at four examinations. The slightest possible trace of albumin was found in one specimen, a few white blood cells and a rare red blood cell were found in the sediments. Blood-pressure: 115/80.

TABLE IV.—OBSERVATIONS ON BLOOD OF CASE IV.

Date.	White cells.	Non-protein nitrogen, mg. per 100 c.c. of blood.	Creatinin, mg. per 100 c.c. of blood.	Uric acid, mg. per 100 c.c. of blood.	Remarks.
1920:					
Jan. 5	39,200	42	1.05	2.7	Before treatment.
Jan. 8	28,200	43	0.96	2.0	
Jan. 10	21,800	36	0.95	3.1	Decided improvement.
Jan. 15	20,000	32	...	3.5	
Jan. 22	12,800	42	...	2.4	No symptoms; lower pole of spleen three fingers' breadth above crest of the ilium.

**Discussion.**—An examination of the results presented above indicates at once that our cases were of very different degrees of severity. Cases I and II, with white counts in the neighborhood of 800,000, suffered from a variety of symptoms of a more or less distressing nature; Cases III and IV were, on the other hand, of a much milder type, the chief complaint in these patients being weakness and occasional nausea.

In view of these facts the different levels attained in the two classes of cases by the non-protein constituents of the blood is of interest. In Cases I and II the initial blood analysis revealed a concentration of 110 and 105 mg. of non-protein nitrogen for 100 c.c. of blood. On the other hand the creatinin content of the blood had not risen above strictly normal limits. Such a result would

appear to suggest the presence in the blood of some abnormal nitrogenous constituent or of an abnormal concentration of some normally occurring substance. In view of the relatively high concentration of amino-acids present in the blood of birds and of other animals whose erythrocytes are nucleated, it occurred to us that this higher value for non-protein nitrogen might be due to the presence of an excessive amount of amino compounds. As it was impossible to obtain an amount of blood sufficiently large for the determining amino nitrogen, we had recourse, of necessity, to an indirect method for the investigation of the problem. To this end we determined the urea in two samples of the blood of Case I. In the first sample, which gave a non-protein nitrogen value of 110 mg. per 100 c.c. of blood, the urea nitrogen amounted to only 22 mg., while in a sample of blood from the same patient, taken after treatment had been carried out for some time, the urea nitrogen amounted to 31 mg., while the non-protein nitrogen had a value of 77.

Lack of material made it impossible, however, to extend this line of investigation to the other cases studied, but it seems safe to at least suggest the hypothesis that these high figures are in all probability not caused by mere retention but are due to the presence in the white cells of some nitrogenous substance or substances not differentiated in our present scheme of micro-blood analysis.

The severity of the symptoms, the high white counts and the high non-protein values seen in Cases I and II, as contrasted with the relative mildness of the symptoms, the relatively small increase in white cells and the moderate increase in non-protein nitrogen found in Cases III and IV is at least suggestive.

The concept of the relation of the white blood cells to nuclear metabolism is so firmly established that the high content of uric acid in the blood of persons suffering from leukemia was recognized even before the advent of modern methods of blood analysis. So far as we are aware, however, no attempt has been made to determine the relation, if any, which may exist between the concentration of white cells and the concentration of uric acid in the blood.

An inspection of the results obtained on our patients indicates absolutely no connection between the white count and the concentration of uric acid; while occasional breaks in the curves occur, it was a matter of considerable surprise to us to find that at the end of the period of observation, when the white count and basal metabolism had both fallen to a fraction of their former values, the uric acid concentration of the blood still remained at its initial height, a finding of interest in view of the results of many of the workers who have examined the urines of leukemia cases under treatment and who have reported large increases in phosphate excretion, accompanied with a practically unchanged uric acid output.

It has been suggested by Myers and Fine<sup>4</sup> that the retention of

uric acid without a corresponding increase in the urea or non-protein nitrogen fractions of the blood may be early evidence of an impairment of renal function. As in our cases there was no clinical evidence of nephritis, we are forced to look elsewhere for an explanation of this phenomenon.

**Summary.** Results are reported on four cases of myelogenous leukemia in which the chemical changes occurring in certain of the non-protein constituents of the blood during roentgen-ray treatment have been followed.

In the more severe cases the non-protein nitrogen was extremely high; after treatment a gradual but steady fall was noted. In view of the fact that the creatinin values are invariably normal and that in our most severe case urea accounted for only 20 per cent. of the non-protein nitrogen fraction (instead of the usual 50 per cent.), the suggestion is made that in leukemia there is present, possibly as a constituent of the white cells, some nitrogenous constituent not accounted for in the present scheme of micro-blood analysis.

The uric acid content of the blood was much increased, but a large diminution in the number of white cells which occurred as a result of treatment caused no appreciable decrease in this constituent.

## CHRONIC LUNG DISEASE FOLLOWING THE INFLUENZA PANDEMIC OF 1918-1919.<sup>1</sup>

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So protean a disease as influenza deserves and also enjoys a most complete literature. Its sequelæ, while not having been neglected by any means, have not been as fully treated as the disease itself, particularly those which require months and sometimes years to clear up. One of the reasons for this lies perhaps in the fact that previous epidemics have been caused by the Pfeiffer bacillus, while in 1918 this organism was rather more conspicuous by its absence than otherwise, with a resulting invasion of the body by an organism or group of organisms of more intense virulence. At any rate it is well remembered how devastating an infection the "flu" was in its incipency and acute stage, and it is not surprising that complete recovery constitutes a slow process in some cases. The purposes of this paper are (1) to present the findings in 12 cases of post-

<sup>1</sup> Arch. Int. Med., 1916, xvii, 570.

<sup>1</sup> Read before the Yorkville Medical Society of New York City, February 16, 1920.



influenzal lung disease, (2) to record a few observations made upon them, and (3) to review some previously reported cases in the literature. It is to be regretted that the great number of patients to be questioned and examined in a dispensary clinic in the relatively short space of time allowed has made it impossible to study these cases as closely as was desirable. They must be shown, therefore, in mere outline:

CASE I.—Mrs. R. G., aged twenty-seven years, Hungarian, No. 3502. Diagnosis: Chronic bronchitis and pleuritis.



FIG. 1.—Case I. Roentgenogram showing shadow at left base, continuous with diaphragm—a thickening of the pleura.

This patient came to the clinic October 10, 1918. Her complaints at that time were cough, with marked expectoration, no blood, severe pain in the chest and back, slight epistaxis, headache, anorexia and weakness in the lower extremities. These were of two weeks' duration since recovery from an attack of influenza. Examination on admission showed a well-nourished woman. Head negative. Heart normal. Lungs showed poor expansion, prolonged expiration, no dulness but scattered dry rales. The diagnosis of chronic bronchitis was made and an expectorant mixture given. Temperature, 98.6° F.; pulse, 88.

May 17, 1919, seven months later, the patient returns complaining of the same symptoms. Heroin given.

June 7 and November 15 the patient's condition is unaltered.

November 22 still has signs of bronchitis.

December 18, patient returns, complaining of severe pain in the chest and back. Cough is now very marked. Brings up thick, yellow mucus. Examination at this time shows dulness at the left apex and slight dulness from the apex to the base on both sides posteriorly, particularly marked on the left side. There are a few crepitant rales at the left apex anteriorly, while posteriorly many moist mucous rales are heard from apex to base, a few pleural rubs being also made out at the extreme left base. Temperature, 99.2° F.; pulse, 80; respirations, 24. Sputum examination for the tubercle bacillus is negative. The roentgen report read as follows: "Roentgen-ray examination of the chest shows a fairly dense shadow at the extreme left base, which is continuous with that of the diaphragm. The roentgen appearance suggests a thickening of the pleura."

CASE II.—Mrs. F. R., aged thirty-eight years, Russian, No. 5690. Diagnosis: pleuritis.

This woman came to the clinic January 25, 1919. Recovered from influenza six weeks ago. Since then she is unable to sleep because of a persistent cough, with pain in the back. No other complaints. Examination revealed a pale, emaciated woman. Teeth poor. Pharynx negative. Heart normal. Lungs showed dulness in small, scattered areas, with signs of a diffuse bronchitis. A few rubs were heard at the left base posteriorly. Heroin and creosote were prescribed.

February 25, patient is not improved.

March 12, complains of severe pain in the left back. The entire left side shows dulness, diminished respiration and diminished voice and whisper.

August 16, still coughing and has much pain in the left back.

December 9, same. Dry cough, no expectoration. There is slight dulness in the left axilla, with increased intensity of the inspiratory murmur. No rales.

December 11, slight expectoration. Pain is much diminished. Signs have almost disappeared. Sputum is negative for the tubercle bacillus.

December 24, "roentgen-ray examination of the chest shows no abnormality in the lungs." This was no doubt a case of post-influenzal pleuritis, which took a whole year to clear up.

CASE III.—Mrs. S. B., aged twenty-nine years, Austrian, No. 5773. Diagnosis: Pleuritis, unresolved pneumonia?

This patient came to the clinic March 29, 1919, complaining for three months of severe pain in the chest on breathing. The pain began directly after recovery from an attack of influenza in January. Patient does not know if it was followed by pneumonia or not. Now has painful cough; no expectoration; no fever. No other symptoms except occasional heartburn. Examination showed a well-nourished woman. Pharynx red. Heart normal. At the right base posteriorly there is dulness, increased intensity of the inspira-

tory and expiratory murmur; no rales but a few rubs. Heroin and terpin hydrate given.

June 26, pain in the chest and back is not relieved.

July 19, restless all last night because of the pain in the chest. Bromides given.

August 17, still has pain. Examination at this time shows again dulness at the right base posteriorly, with increased intensity of the inspiratory and expiratory murmurs and a few rubs.

August 9, the roentgen report read as follows: "Roentgen-ray examination of the chest shows lessened aëration of the right lung, with marked density at the right base, which may be evidence of a thickened pleura or traces of an unresolved pneumonia." No sputum obtainable in this case. Temperature normal.

CASE IV.—Mrs. R. D., aged thirty-six years, Russian, No. 5822. Diagnosis: Chronic bronchitis.

This patient came to the clinic May 10, 1919. Had influenza four months ago. Since then she has been coughing and expectorating thick, yellow mucus. Pain in the chest and back is marked. "Gets a cold" very easily, making it necessary for her to be in bed for three or four days at a time. Thinks she has slight fever now. Feels very weak. Examination showed a young woman, well-nourished, coughing. Many teeth missing. Pharynx normal. Heart normal, but very rapid action. Lungs showed dulness at the right apex anteriorly and at both bases posteriorly, with coarse, moist rales at the end of inspiration. Temperature, 99° F.; pulse, 92. Urine negative. Sputum examination for the tubercle bacillus negative. Expectorant mixture given.

December 16, returns complaining of slight pain in the chest and slight cough. There is slightly increased intensity to the breath sounds at the left base posteriorly, but no dulness or rales. Patient is practically well.

CASE V.—Mrs. M. Z., aged twenty-eight years, Russian, No. 5831. Diagnosis: Chronic bronchitis.

This patient first appeared in the clinic on May 17, 1919. She did not return for further study. Her complaint was that since an attack of influenza, with pneumonia, the winter before she had not been at all well. There was headache, dyspnea on exertion, marked pain in the chest, cough but with scant expectoration. A few days previous to her visit to the clinic these symptoms had suddenly become worse. Examination showed a young woman not acutely ill apparently. Head normal. Pharynx normal. Pyorrhea alveolaris. Faint apical, non-transmitted, purring systolic murmur, but the heart was otherwise normal. Lungs showed slight dulness at both apices, with roughened inspiration and an occasional mucous rale. Expectorant mixture given. Urine negative. Temperature, 99.4° F.; pulse, 88; respirations, 24. No sputum obtainable.

CASE VI.—Mrs. S. G., aged forty-one years, American, No. 5832. Diagnosis: Pleuritis, unresolved pneumonia.

This patient came to the clinic May 20, 1919. Had influenza, followed by pneumonia, one year ago. Was in Mount Sinai Hospital for nine months. Pain in the chest, which followed, has not yet disappeared. Cough marked. Brought up blood last night. Flushes easily. Headache. No vomiting. Bowels costive. Examination showed a well-nourished woman. Face flushed. Pharynx negative. Teeth false. Small simple goiter. Heart normal except for a faint, non-transmitted apical systolic murmur. Labile pulse. Lungs: Left base showed dulness, roughened inspiration but no rales. Right base showed dulness, decreased respiration by measure and sound and increased vocal fremitus. Bronchophony at the spine opposite the middle of the scapula. Tender liver edge was palpable. Left lumbar scoliosis. Reflexes exaggerated. Temperature, 99° F.; pulse, 80; respirations, 24. Creosote and heroin given.

May 20, "Roentgen-ray examination of the chest does not show any definite abnormality in the lungs. It should be stated, however, that owing to the marked scoliosis of the lumbar spine, with a resulting deformity of the chest, it is very hard to interpret the plates." Sputum negative for the tubercle bacillus. Urine negative.

December 2, still coughs and has pain in the chest. Examination at this time shows dulness at the left base but no rales. The bronchophony has disappeared.

December 9, a second roentgen ray "does not show any definite abnormality in the lungs."

December 16, still has slight cough and pain in the chest. On examination there is nothing abnormal except a slight dulness at the left base.

CASE VII.—Mrs. M. R., aged twenty-three, Russian, No. 5841. Diagnosis: Chronic bronchitis.

This patient appeared in the clinic May 27, 1919. Since recovery from influenza last February has been having slight cough, without expectoration, marked pain in the chest, poor appetite and weakness. Examination showed a well-preserved young woman. No abnormality except high-pitched voice and breath sounds at the left base posteriorly. Heroin given.

June 3, same.

June 6, same.

September 9, complains of severe pain in the left chest. Strapped.

September 18, still has pain in the chest. Examination shows roughened inspiration, with an occasional mucous rale at both bases.

October 28, "roentgen-ray examination of the chest does not show any definite abnormality in the lungs." No sputum obtainable.

CASE VIII.—Mrs. K. S., aged forty-six years, Russian, No. 5880. Diagnosis: Pleuritis, unresolved pneumonia.

This patient came to the clinic June 26, 1919. Influenza five months ago. Still has pain in the left chest. Headache. Coughed up blood yesterday. Cough is not frequent, however. No other complaints. Examination is negative except for the presence of dulness and fine, moist, crackling rales at the left base posteriorly at the end of inspiration. Heroin and creosote given. Sputum is negative for the tubercle bacillus.

July 15, feels somewhat better.

July 18, had an hemoptysis yesterday. Feels dizzy.

August 14, "Roentgen-ray examination of the chest shows neither of the bases to appear clear, but there does not seem to be any definite sign of effusion. The right diaphragm shows two adhesions."

September 9, pain same but cough is lessened.

November 16, same. Has not returned to the clinic since.

CASE IX.—Mrs. T. S., aged twenty-six years, Russian, No. 5933. Diagnosis: Pleuritis, asthma.

This patient came to the clinic August 9, 1919. Had a severe attack of influenza last February. Since then feels weak and dizzy. Marked palpitation on exertion. Pain in the chest, boring through to the back. Cough but no expectoration. Poor appetite. Examination reveals a poorly nourished woman. The rest of the examination is negative except for the lungs, which show dulness with roughened inspiration at both bases posteriorly but no rales. Creosote given.

September 19, very weak. Maltine with hypophosphites.

September 23, strychnin sulphate.

November 1, "Roentgen-ray examination of the chest shows a shadow at the extreme left base just above the diaphragm. This is probably due to a thickening of the pleura." Heroin.

November 6, same pain, great difficulty in expiration yesterday. Examination shows prolonged expiration and many musical rales all over the chest and back. A mixture containing belladonna, spirits of ether and potassium iodide was given.

December 13, patient feels better. Second roentgen ray shows at this time "no abnormality in the lungs."

December 16, dulness and roughened inspiration at the left base still present, but the musical rales and prolonged expiration have disappeared. Sputum negative for the tubercle bacillus.

CASE X.—Mrs. C. G., aged thirty years, Russian, No. 5968. Diagnosis: Pulmonary tuberculosis.

This patient came to the clinic September 6, 1919, complaining of cough for one year. It began two months after recovery from influenza. Still coughs. Blood-streaked sputum three weeks ago. Pain in the chest is sometimes localized to the left apex. Headache, weakness and anorexia. No night-sweats, fever, or loss in weight.

Examination showed a slight goiter. The lungs showed dulness and many moist rales at the left base. There were fine crepitations and increased voice and whisper at the apices anteriorly.

September 9, blood-streaked sputum for the past two days. Creosote given.

September 11, roentgen-ray examination of the chest shows small tuberculous cavities at the apices. Sputum shows the tubercle bacillus. The patient was referred to the tuberculosis clinic for treatment.

CASE XI.—Mrs. D. W., aged sixty-three years, Roumanian, No. 5987. Diagnosis: Tuberculous mediastinitis.

This patient came to the clinic September 18, 1919. Had grippe six months ago and also one month ago. Complains of pain in the chest for the past two weeks and marked cough for six months. Cough worse of late. No expectoration. Headache. No loss in weight. Her menopause occurred at the age of forty-eight. Examination showed an old woman. Teeth false. Bulge of chest to the left. Dulness to flatness on both sides of midsternal line. Suprasternal veins enlarged. Heart enlarged to the left by percussion. No apex-beat visible or palpable. No murmurs. A2 exaggerated. Lungs showed dulness at the right apex anteriorly and at the left base posteriorly, with bronchovesicular respiration in the left axilla and base. No sputum obtainable. The urine was normal.

September 18, "roentgen-ray examination of the chest shows a considerable number of infiltrations in both upper lobes, extending down to the level of the second rib on the right and the third rib on the left. The roentgen appearance is that of a tuberculous process. There appears to be also some mediastinal involvement."

CASE XII.—Mrs. K. G., aged forty-one years, Russian, No. 6236. Diagnosis: Pulmonary tuberculosis; enlarged aorta.

This patient came to the clinic December 16, 1919, complaining of pain in the chest for the past few months. This began shortly after an attack of the "flu" in March, 1919. Spits up blood. Short of breath. Feels sore beneath the sternum. Pain in the sides. Coughs considerably. Has headaches. Bowels costive. No urinary disturbances. Examination showed a fairly well-nourished and developed woman whose expression is worried. Pharynx reddened. Tonsils not enlarged. Teeth poor. Thyroid negative. Pulsation in the neck and over the upper sternum, with marked dulness in this region. Impure second aortic sound. Heart is not enlarged, however. Lungs show dulness at the apices anteriorly and also down to the angles of the scapulæ posteriorly. At the left apex there is increased intensity to the voice and whisper, while at the right a few fine, crackling rales with bronchovesicular respiration, may be heard.

December 16, "roentgen-ray examination of the chest shows an extensive bilateral tuberculosis extending to the level of the fourth

rib anteriorly. There appears to be, in addition, a hypertrophy of the left ventricle. The aorta is moderately enlarged."

December 23, hemoptysis is not so marked this week. Same signs. Sputum could not be obtained.

## SUMMARY OF CASES.

Case.	Date of influenza.	Diagnosis.	Nutrition.	Fever.	Sputum.	Röntgen-ray findings.	Result, Jan. 1, 1920.
1	Oct., 1918	Pleuritis; chronic bronchitis	Good	None	Thick; no tubercles	Shadow at left base; a thick pleura	Same.
2	Jan., 1919	Pleuritis	Poor	"	No tubercles	Not taken	Much improved.
3	Jan., 1919	Pleuritis; unresolved pneumonia?	Good	"	None	Shadow at right base	Same.
4	Feb., 1919	Chronic bronchitis	"	"	Thick; no tubercles	Not taken	Well.
5	"Last winter"	Chronic bronchitis	"	"	None	Not taken	Well.
6	May, 1918	Pleuritis; unresolved pneumonia?	"	"	Bloody; no tubercles	Negative	Much improved.
7	Feb., 1919	Chronic bronchitis	"	"	None	Negative	Much improved.
8	Feb., 1919	Pleuritis; unresolved pneumonia?	"	"	Bloody; no tubercles	Bases cloudy; adhesions to diaphragm	Much improved.
9	Feb., 1919	Pleuritis	Poor	"	Slight; no tubercles	Thickened left pleura	Asthma.
10	July, 1918	Pulmonary tuberculosis	"	"	Bloody; tubercles positive	Small cavities in both apices	Poor health.
11	May, 1919	Tuberculosis; mediastinitis	"	"	None	Infiltrations in both apices	Poor health.
12	Mar., 1919	Tuberculosis; enlarged aorta.	Good	"	Bloody; no tubercles	Infiltrations in both apices; enlarged aorta; left ventricle hypertrophy	Poor health.

In all cases, except Case 10, the symptoms for which the patients sought relief began directly after the attack of influenza; in Case 10 they began two months after.

There were several other cases (about seven) whose cough, pain in the chest and back, dyspnea and palpitation on exertion and history of a preëxisting influenza attack made it almost morally certain that they, too, belonged in this group, but they were excluded because of insufficient clinical evidence to warrant the diagnosis of chronic lung disease. An analysis of the foregoing chart reveals the following interesting facts:

1. The duration of the lung disease was in 3 cases over one year, in 2 cases eleven months, in 5 cases ten months and in the remaining 2 cases about eight months.

2. The lesion present was in 6 cases pleuritis—3 of which probably also had unresolved pneumonia; in 3 cases chronic diffuse bronchitis and in the remaining 3 cases pulmonary tuberculosis.

3. In all but 3 cases the pathological process was at the bases of the lungs. These 3 were tuberculous cases.

4. Sputum was absent in the pleuritis cases as a general rule and

copious in the bronchitis cases. Hemoptysis occurred 4 times, but the tubercle bacillus could be found in only 1 case.

5. The pain occupied wide areas. Often the patient swept her hand from apex to base in describing it. Localized pain occurred only once (Case X). This patient was tuberculous.

6. Fever was absent altogether.

7. The nutrition was poor in but 4 cases; 2 of them were tuberculous. Despite the asthenia, of which the patients complained so much, they were able to keep up their general nutrition.

8. A lapse of an average of ten months, after the original influenza, has left 2 patients well, 2 unchanged, 3 tuberculous and in poor



FIG. 2.—Case XII. Roentgenogram showing bilateral, apical tuberculosis, hypertrophy of the left ventricle and enlargement of the aortic arch.

health; 1 slightly asthmatic, but otherwise much improved and the remaining 4 much improved. The only ones in which improvement was lacking were the tuberculous cases. In the others it was the rule, but very slow in coming about.

9. Creosote and heroin gave the best results in the treatment.

The pathology of this series was comparatively simple—pleurisy with possibly unresolved pneumonia, chronic bronchitis and pulmonary tuberculosis. The latter lesion was at the apices and the former ones at the bases. During the epidemic proper it was not so simple, however. Huge multiple abscesses, interlobar collections of pus, copious empyemata, wide areas of consolidation in odd parts



of the lungs, thick pleurisies and mushy gangrene of the lungs were not infrequent. Chronic effects from such lesions were to be expected in some cases which recovered.

Neuhof and Davidson<sup>2</sup> have found by systematic fluoroscopic examinations of many patients with pneumonia during convalescence that there were distinct shadows present over the localized areas of preëxisting consolidation for some weeks after the crisis. This was interpreted by them to mean that complete resolution in pneumonia did not take place for weeks and the physical signs of localized bronchitis might mean incomplete resolution even when the signs of consolidation had disappeared.

Feissinger,<sup>3</sup> in 1889, saw 126 cases of influenza in children and described 2 cases of chronic pulmonary congestion. One was that of a boy, aged seven years, who on the twelfth day of the disease had a fall in temperature, but a subsequent rise each evening. There was dulness, markedly diminished respiration and rubs at the right base posteriorly. Occasionally subcrepitant rales were heard over this area, but they were most frequently absent. Complete resolution took place fifty-two days after the onset of the disease. The second was that of a girl, aged five years, who had practically the same signs, which did not clear up until the sixty-first day: Eshner,<sup>4</sup> in 1894, cites a case of endocarditis and pleuritis following influenza in a male, aged twenty-five years, which took two years to recover from. The entire left side was involved. Morel-Lavallée,<sup>5</sup> in 1897, describe several cases of dry pleurisy following influenza. There was in a few no discomfort, but in the majority cough and pain in the chest were severe. There was no fever. Epistaxis occurred in 3 cases and dyspnea such as is seen in toxic conditions. An average of five weeks was required to recover from the pleurisy. In 1902, Lord<sup>6</sup> reported the clinical findings in 18 cases of chronic influenza in whom bacteriological examination of the sputum revealed the Pfeiffer bacillus in every case. Repeated examinations of the sputum for the tubercle bacillus were negative. The material was from the male outpatient department of the Massachusetts General Hospital. According to Lord the pathology of these cases—no autopsies were obtainable—is probably small patches of original bronchopneumonia, which break down into small abscesses, the constant discharge from which

<sup>2</sup> Clinical Survey of Acute Pulmonary Affections of 1916, New York Med. Jour., June 2, 1917.

<sup>3</sup> De la Congestion Pulmonaire Chronique Consécutive à la grippe, Gaz. méd. de Paris, December 14, 1889, vi, 592-594.

<sup>4</sup> Influenza Followed by Pleuritis and Endocarditis, Med. News, Philadelphia, 1894, lxiv, 148.

<sup>5</sup> Pleurésie Sèche Bilatérale d'origine Grippale, Bull. et mém. Soc. des hôp. de Paris, 1897, 3 s., xiv, 1369-71.

<sup>6</sup> Eleven Acute and Eighteen Chronic Cases of Influenza Proved by Bacteriological Examination, Boston Med. and Surg. Jour., December 18, 1902, No. 25, clxvii, 659-669.

induces a chronic bronchitis. Of the 18 the physical signs showed in 10 cases diffuse bronchitis, bilateral apical bronchitis in 1, nothing abnormal in 2, repeatedly recorded signs of consolidation at the left base in 1, and in the remaining 4 cases the diagnosis of bronchial asthma was made. He believes that these 4 were really suffering from paroxysmal dyspnea. No Curschmann spirals or Charcot-Leyden crystals were present in the sputum, and eosinophiles were absent from the blood. He thinks that emphysema and even bronchiectasis may be caused by so much coughing.

In 1909, Franke<sup>7</sup> studied a large series of cases in Berlin. Fever was absent. Blood counts made in 100 cases showed normal figures. Hemoglobin was from 75 per cent. to 80 per cent. Urine occasionally showed albumin, but in the majority it was normal. The usual asthenic symptoms were present. Neuralgic pains in the back, chest and limbs were persistent and due to neuritis. Franke warns against diagnosing pleurisy, endocarditis, renal colic, appendicitis or any other painful condition without first eliminating this neuritis. Two signs in chronic influenza worked by himself are (1) beefy redness and dryness of the soft palate, and (2) corrugation of the tongue with enlargement of the organ and hypertrophy of the anterior papillæ. Of lung signs, showers of rales in various parts of the lungs were most frequent. They occasionally disappeared with heroin or codein, only to return on discontinuance of its use. These cases he regarded as tuberculous, but the tubercle bacillus could not be found in the sputum.

The question of tuberculosis following influenza is a difficult one to be positive about. To attempt to establish a basis for the differential diagnosis between tuberculous and other forms of lung disease by means of the observations noted in the 12 cases in the series of this paper is obviously both unscientific and useless. A very definite statement in this connection is made by Fishberg,<sup>8</sup> under whose observation may hundreds of cases of the so-called "flu" have come, both during the epidemic of 1918 and much later. His position is best stated by the following quotation: "Contrary to the teachings of writers of previous generations the recent epidemic of influenza has shown that this disease is not etiologically related to tuberculosis. Of the hundreds of cases which have come under my observation during the past year in which cough, expectoration, fever etc., have persisted after an attack of influenza, only one turned out to be tuberculosis. The pulmonary sequelæ of influenza are hardly ever tuberculous in character. Most of these patients suffer from bronchitis, bronchiectasis, pleurisy, abscess of the lung, etc. They should not be banished to distant climes or sanatoriums."

<sup>7</sup> Ueber Chronische Influenza, Wien. u. Leipzig, Urban, 1909, pp. 203-232; in Beihefte z. med. Klinik, j, 9 h. 10.

<sup>8</sup> Diagnostic Pitfalls in Pulmonary Tuberculosis, New York Med. Record, January 17, 1920, No. 3, xcvi, 89-94.

It will be seen, then, that chronic lung disease following influenza is not so uncommon and that it is easy to say "tuberculosis," but it is a very hard thing to prove.

I wish to express my thanks to Dr. Jaches, to Dr. Wessler and to Dr. Lund, roentgenologists to the Mount Sinai Hospital, for their kindness and coöperation in the roentgen-ray department; and to Dr. Friedman and to Dr. Weiss, my colleagues in the clinic, for referring their cases to me.

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## PNEUMONIA AT A BASE HOSPITAL, 1918-19.

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THIS is an account of my personal observations of pneumonia at the Base Hospital, Fort Sam Houston, Texas, during the season 1918-19, of cases which were under my immediate control and treated and studied by me personally. A series of 137 cases were admitted to my ward without selection, picked up in the different influenza wards and diagnosed pneumonias; thus I think that they represent fairly well a picture of the type of pneumonia we had to deal with during the epidemic. Some of the cases were moribund when admitted, but most of them were diagnosed early, so that the study in the majority of cases began at the early stage of the pneumonic process. Much care was given to the working out of the bacteriology of each individual case as well as the clinical aspects of the disease. With the splendid coöperation of the laboratory and the adequate nursing facilities I was enabled to carry on this work to the end of the epidemic. I wish to express my hearty thanks to all those who took an enthusiastic part in this work. Miss King did the blood chemistry on cases studied.

In the study of the sputa and the throat swabs the request was always made out for the four types of organisms, viz.:

1. *Pneumococcus* type.
2. *Streptococcus hemolyticus*.
3. *Influenza bacillus*.
4. *Micrococcus catarrhalis*.

Thus the accompanying tables have "plus" for positive and "minus" for none present. Here, however, I must state that the special media for the cultivation of the *Bacillus influenzae* as described by Avery, of the Rockefeller Institute for Medical Research in the *Jour. Am. Med. Assn.*, lxxi, 2050, was not used, which may answer for our very low percentage of the *Bacillus influenzae* found.

**BACTERIOLOGICAL VARIETIES PRESENT.** The diagram shows the incidence of the various types of pneumococci isolated from the sputum. The sum total of these various types represents 43.8 per cent. It is difficult to say whether or not a pneumococcus found in sputum represents lobar pneumonia. There were some cases which were lacking a frank lobar consolidation in which we did isolate pneumococci from the sputum. Should these be classed as lobar pneumonias? This has always been a question in my mind, the exact status of what constitutes a lobar pneumonia, whether a frank consolidation with pneumococci found in sputum or even a partial consolidation or patchy consolidation with a pneumococcus recovered from the sputum or the blood stream.

Pneumonias here described followed influenza. Just what percentage of them I am unable to say. The diagnosis of influenza in some of these cases I have questioned; thus I hardly think it would be accurate to try to give the percentage of cases that followed influenza. Let us say that the majority had influenza preceding pneumonia.

The bronchopneumonias with the etiological factor of *Streptococcus hemolyticus* made up 36.7 per cent. Some of these cases later in the disease went into massive consolidation, described by McCallum and Cole last year, with pleural effusions and a very high mortality, which in these cases was 83.3 per cent. It is of interest to note that of the 30 cases from which *Streptococcus hemolyticus* was isolated from the sputum it was found in the blood stream 13 times and it was not found 17 times. Of the positive blood cultures here 92.3 per cent. died, whereas only 57.64 per cent. died with the negative blood cultures.

The influenza bacillus recovered from the sputum composed only 2.4 per cent. The low percentage of the influenza bacilli found may be due to several causes:

1. The cases were not early influenza, only coming into this group after pneumonia developed.

2. Cultures were made on ordinary blood agar, the special media described by Avery, of the Rockefeller Institute, not having at this time been in use.

3. No special effort was made by repeated examinations to find *Bacillus influenzae*.

*Micrococcus catarrhalis* represents 17.1 per cent. There were no deaths in this series.

The clinical picture of both the lobar and the bronchopneumonias has been described too many times by the different observers, and I shall not add to the numerous repetitions, for our cases did not differ in this aspect from those at other places. I have already described these sufficiently in another paper.

The bacteriology of throat cultures represents one important

point, *i. e.*, that *Streptococcus hemolyticus* is present in a large number of the cases, 42 per cent. This undoubtedly is a potent factor in the subsequent production of the hemolytic streptococcus pneumonias and its incidental high death-rate. *Streptococcus hemolyticus* found in the throat and subsequently in the sputum was present in 13 cases.

*Streptococcus hemolyticus* found in the throat and not isolated from the sputum occurred in 9 cases.

*Streptococcus hemolyticus* found in the throat and not found in the sputum, but again recovered from the blood stream, occurred in 1 case.

#### OCCURRENCE OF VARIOUS TYPES OF ORGANISMS IN SPUTUM.

Type of organism.	Incidence.	
	Number.	Per cent.
<i>Pneumococcus</i> , Type I . . . . .	2	2.4
<i>Pneumococcus</i> , Type II . . . . .	1	1.2
<i>Pneumococcus</i> , Type IIa . . . . .	5	6.0
<i>Pneumococcus</i> , Type III . . . . .	2	2.4
<i>Pneumococcus</i> , Type IV . . . . .	26	31.8
<i>Streptococcus hemolyticus</i> . . . . .	30	36.7
<i>Influenza bacillus</i> . . . . .	2	2.4
<i>Micrococcus catarrhalis</i> . . . . .	14	17.1
Total . . . . .	82	100.0

#### OCCURRENCE OF VARIOUS TYPES OF ORGANISMS IN THE THROAT.

Type of organism.	Incidence.	
	Number.	Per cent.
<i>Pneumococcus</i> . . . . .	0	
<i>Streptococcus hemolyticus</i> . . . . .	21	42
<i>Influenza bacillus</i> . . . . .	2	4
<i>Micrococcus catarrhalis</i> . . . . .	27	54
Total . . . . .	50	100

RELATION OF TYPES OF ORGANISMS IN SPUTUM TO MORTALITY. The death-rate in this series was 27.73 per cent. against 18.19 per cent. in the 819 cases reported in the previous paper, which represents all the pneumonia cases here last winter. One factor here is of importance, and that is that this series deals with 36.5 per cent. of *Streptococcus hemolyticus* against 25.1 per cent. in the other series. Furthermore, some cases were sent up when they were already moribund which in itself would raise the percentage considerably in a small series of cases.

In the incidence of various organisms in the sputa to the mortality, *pneumococcus* type III takes the lead together with *Streptococcus viridans*, both representing a mortality of 100 per cent. *Strep-*

tococcus hemolyticus comes next with a mortality of 83.3 per cent., pneumococcus type IIa with a 40 per cent. mortality and pneumo-

FIG. 1.—Occurrence of various types of organisms in sputum.

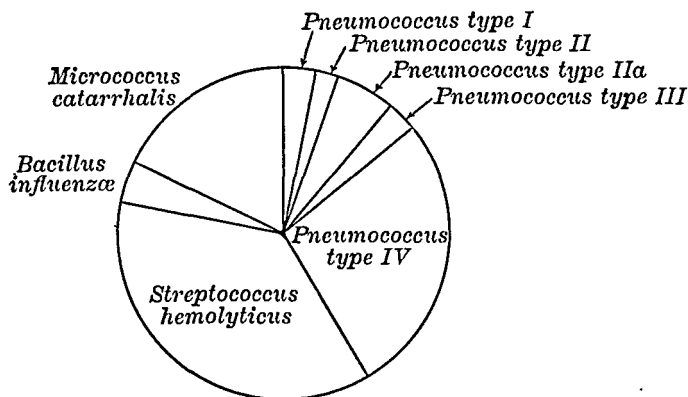


FIG. 2.—Occurrence of various types of organisms in throat.

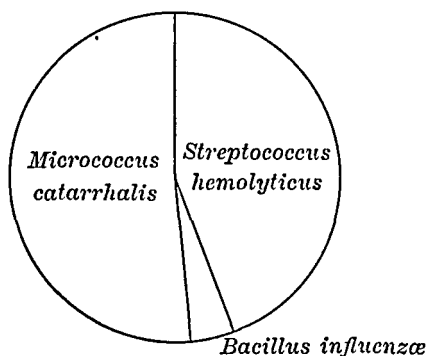
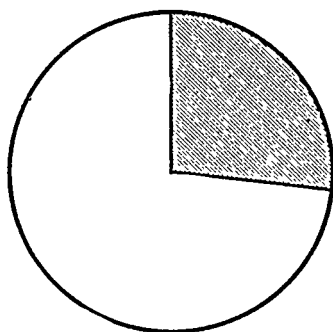
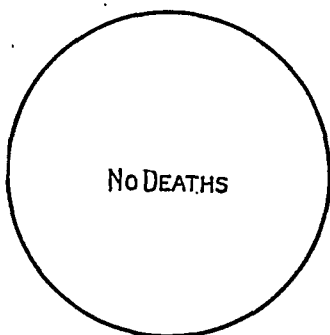


FIG. 3.—Total death-rate. Total number of cases, 137; died, 38; percentage, 27.73.

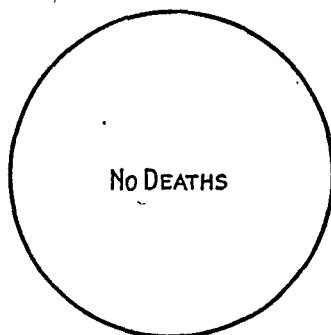


coccus type IV with 7.6 per cent. There was no mortality in the pneumococcus type I and II infections and also in the *Bacillus influenzae* and *Micrococcus catarrhalis*.

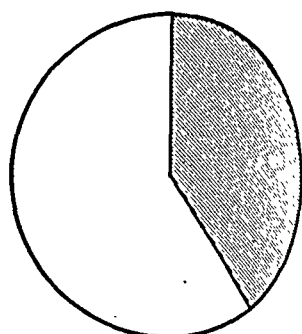
FIG. 4.—Death-rate from various organisms recovered from sputum.



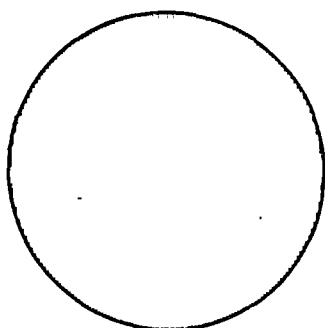
Pneumococcus, Type I:  
Total number of cases,  
2; deaths, 0.



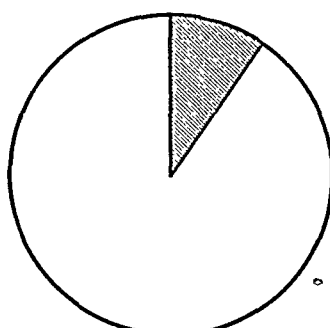
Pneumococcus, Type II:  
Total number of cases,  
1; deaths, 0.



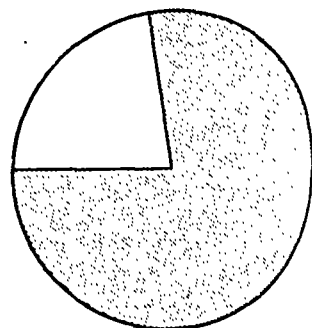
Pneumococcus, Type IIa:  
Total number of cases, 5;  
deaths, 2; percentage, 40.



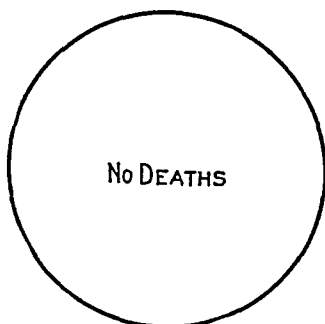
Pneumococcus, Type III:  
Total number of cases,  
2; deaths, 2; percentage,  
100.



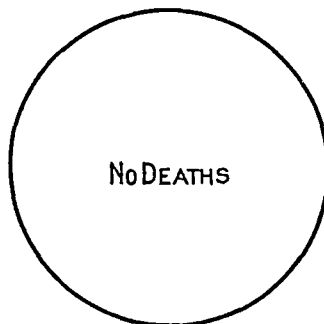
Pneumococcus, Type IV:  
Total number of cases,  
26; deaths, 2; percentage,  
7.6.



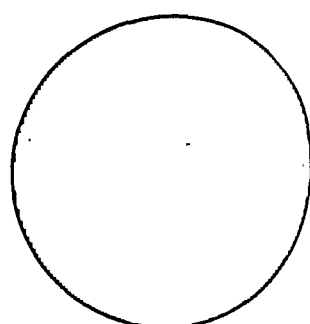
Streptococcus hemolyticus:  
Total number of cases,  
30; deaths, 25; percent-  
age, 83.3.



Bacillus influenzae: Total  
number of cases, 2;  
deaths, 0.



Micrococcus catarrhalis:  
Total number of cases,  
14; deaths, 0.



Streptococcus viridans:  
Total number of cases,  
1; deaths, 1; percent-  
age, 100.

The fact that *Streptococcus hemolyticus* is a very virulent infection is only emphasized in these tables.

#### INCIDENCE OF VARIOUS TYPES OF ORGANISMS IN SPUTUM AND RESULTING MORTALITY.

Type of organism.	Incidence.		Mortality.	
	No.	Per cent.	No.	Per cent.
Pneumococcus, Type I . . . .	2	2.4	0	0
Pneumococcus, Type II . . . .	1	1.2	0	0
Pneumococcus, Type IIa . . . .	5	6.0	2	40.0
Pneumococcus, Type III . . . .	2	2.4	2	100.0
Pneumococcus, Type IV . . . .	26	31.7	2	7.6
<i>Streptococcus hemolyticus</i> . . . .	30	36.5	25	83.3
<i>Influenza bacillus</i> . . . . .	2	2.4	0	0
<i>Micrococcus catarrhalis</i> . . . .	14	17.0	0	0
<i>Streptococcus viridans</i> . . . . .	..	..	1	100.0
Undetermined . . . . .	..	..	6	

RELATION OF BLOOD CULTURES TO PNEUMONIA. The total number of blood cultures taken was 163. This represents, as can be seen in the diagram, repeated cultures on some patients while a few of the patients were omitted. However, the percentage recorded is on cases and not on individual cultures taken, thus representing a positive if one out of several cultures was positive and negative only where after repeated cultures all were negative.

One fact stands out in prominence here, and that is the very high mortality in cases in which a *Streptococcus hemolyticus* was recovered from the blood stream. Of these 92.3 per cent. died.

In fact this seemed about the only organism which we could recover from the blood stream with the exception of the pneumococcus type IV and 2 cases in which the laboratory was unable to identify the organism.

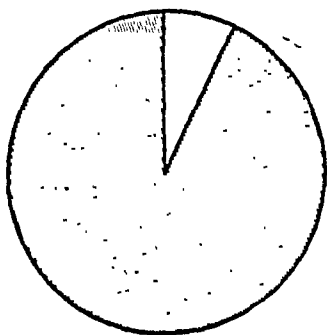
The percentage of deaths with negative blood cultures exceeds the percentage with positive blood cultures by 29.42 per cent.

#### RELATION OF POSITIVE BLOOD CULTURES TO MORTALITY IN PNEUMONIA.

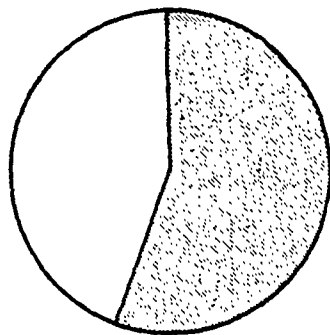
Type of organism in sputum.	No. of cases.	Blood cultures.				Mortality.			
		Positive.		Negative.		Cases with positive blood cult.		Cases with negative blood cult.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
<i>Streptococcus hemolyticus</i> . . . .	30	13	43.30	17	56.70	12	92.30	10	57.64
Pneumococcus:									
Type IV . . . . .	26	1	3.80	25	96.20	..	..	2	8.00
Type III . . . . .	2	..	..	2	..	..	..	..	..
Type IIa . . . . .	5	..	..	5	..	..	..	2	40.00
Type II . . . . .	1	..	..	1	..	..	..	..	..
Type I . . . . .	2	..	..	2	..	..	..	..	..
<i>Influenza bacillus</i> . . . . .	2	..	..	2	..	..	..	1	50.00
<i>Micrococcus catarrhalis</i> . . . .	14	..	..	14	..	..	..	1	7.14
No organism identified . . . . .	55	2	7.60	53	92.40	..	..	6	5.66
Total . . . . .	137	16	11.67	95	88.33	12	35.29	22	64.71



FIG. 5.—Blood culture death-rate. *Streptococcus hemolyticus*.

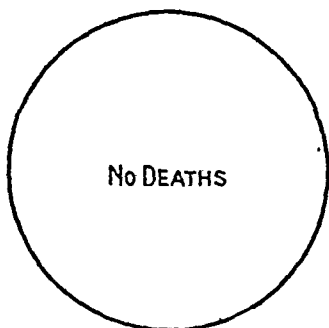


Total number of positive blood cultures, 13; died, 12; percentage, 92.3.

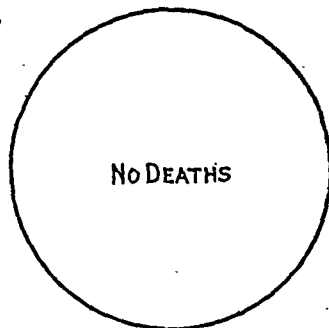


Total number of negative blood cultures, 17; died, 10; percentage, 57.64.

*Pneumococcus*, Type I.

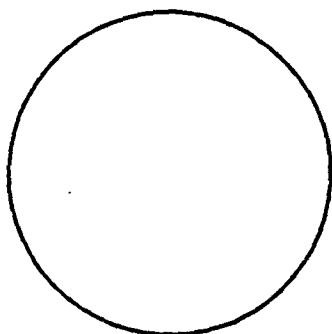


Total number of positive blood cultures, 0.

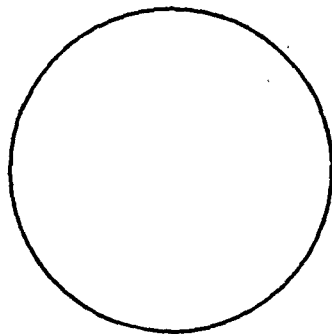


Total number of negative blood cultures, 2; died, 0.

FIG. 6.—Blood culture death-rate. *Pneumococcus*, Type II.

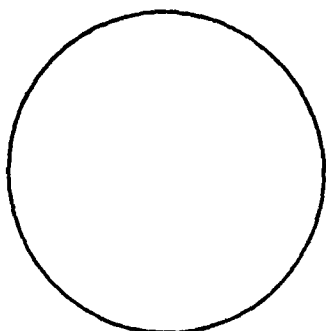


Total number of positive blood cultures, 0.

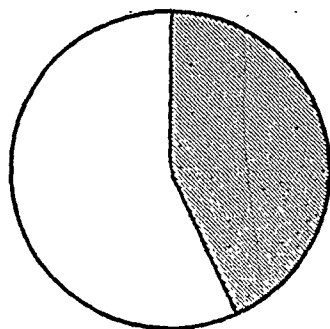


Total number of negative blood cultures, 1; died, 0.

*Pneumococcus*, Type IIa.

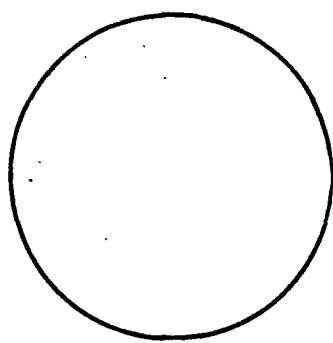
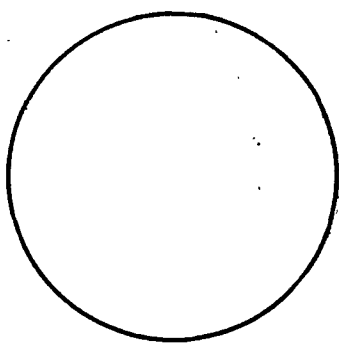


Total number of positive blood cultures, 0.



Total number of negative blood cultures, 5; died, 2; percentage, 40.

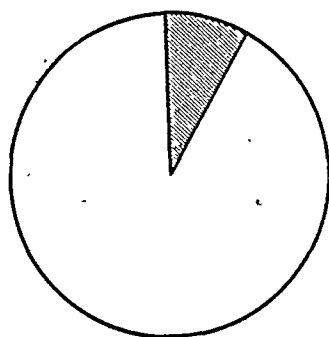
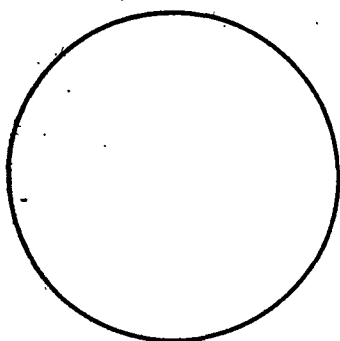
FIG. 7.—Blood-culture death-rate. *Pneumococcus*, Type III.



Total number of positive blood cultures, 0.

Total number of negative blood cultures, 2; died, 0.

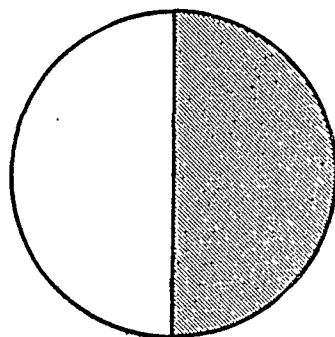
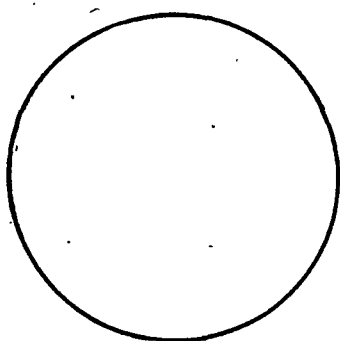
*Pneumococcus*, Type IV.



Total number of positive blood cultures, 1; died, 0.

Total number of negative blood cultures, 25; died, 2; percentage, 8.

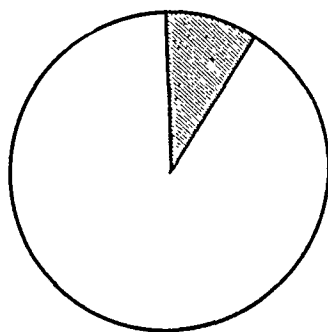
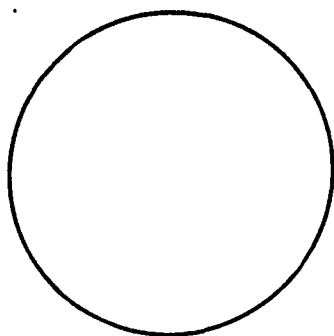
FIG. 8.—Blood-culture death-rate. *Bacillus influenzae*.



Total number of positive blood cultures, 0.

Total number of negative blood cultures, 2; died, 1; percentage, 50.

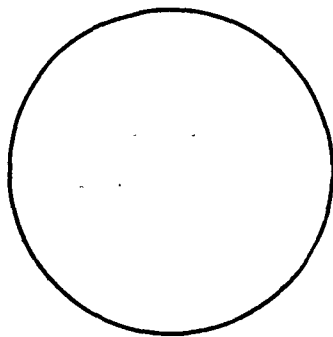
*Micrococcus catarrhalis*.



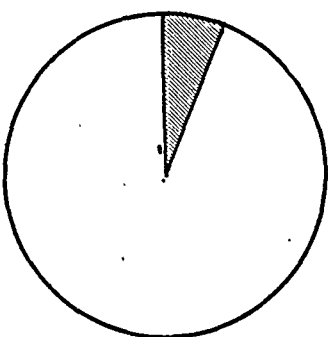
Total number of positive blood cultures, 0.

Total number of negative blood cultures, 14; died, 1; percentage, 7.14.

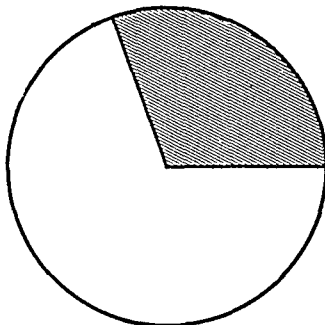
FIG. 9.—Blood culture death-rate.  
Organism not identified.



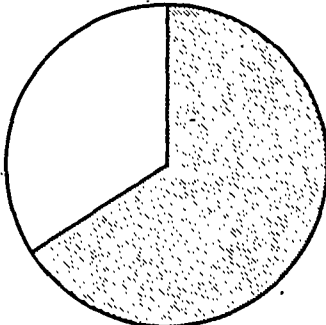
Total number of positive blood cultures, 2; died, 0.



Total number of negative blood cultures, 53; died, 6; percentage, 5.66.



Total number of cases with positive blood cultures: 35.29 per cent.



Total number of cases with negative blood cultures: 64.71 per cent.

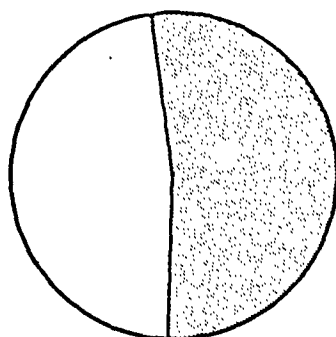
RELATION OF LEUKOCYTES TO MORTALITY. A glance at the diagrams tells the story which has been emphasized so many times during the present epidemic, *i. e.*, that leukocytosis is a very favorable factor in the prognosis of pneumonia.

In the leukocyte count under 10,000, 51.3 per cent. died. In 10,000 to 20,000 only 40.6 per cent. In 20,000 to 30,000 only 8.1 per cent. This needs no comment.

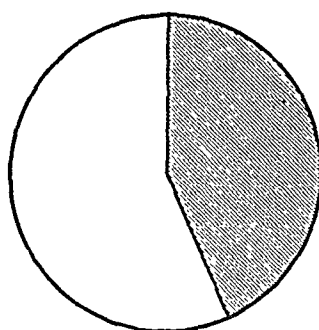
THE RELATION OF LEUKOCYTES TO MORTALITY IN PNEUMONIA.

Leukocytes.	Number of cases.	Mortality. Per cent.
Under 10,000 . . . . .	19	51.3
10,000 to 20,000 . . . . .	15	40.6
20,000 to 30,000 . . . . .	3	8.1
Total . . . . .	37	100.0

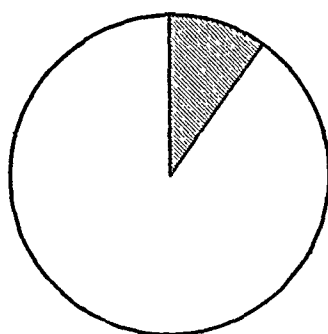
FIG. 10.—Relation of leukocytes to mortality.



Under 10,000: Total number of cases, 19; died, 51.3 per cent.



10,000 to 20,000: Total number of cases, 15; died, 40.6 per cent.



20,000 to 30,000: Total number of cases, 3; died, 8.1 per cent.

COMPLICATIONS. By far the greatest incidence of complications are the pleural effusions, making in this series a total of 78.57 per cent. of all the complications. The total incidence of complications is 30.65 per cent. These tabulated are as follows:

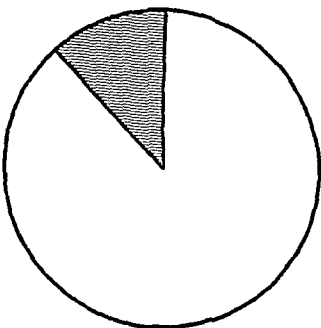
Pleural effusions . . . . .	33
Tonsillitis . . . . .	2
Prostatitis . . . . .	1
Pericarditis . . . . .	1
Sinusitis, frontal . . . . .	1
Lung abscess . . . . .	1
Suppurative perithyroiditis ( <i>Streptococcus hemolyticus</i> ) . . . . .	1
Otitis media . . . . .	2
Total . . . . .	42
	or 30.65 per cent.

VARIETIES OF ORGANISMS FOUND IN THE PLEURAL EFFUSIONS.

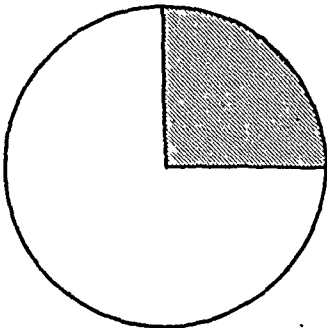
		Per cent.
Total number of effusions . . . . .	33	
Sterile . . . . .	6	18.19
Organisms found in . . . . .	27	81.81
Of these there were:		
Streptococcus hemolyticus . . . . .	19	70.39
Streptococcus viridans . . . . .	1	3.70
Pneumococcus, Type IV . . . . .	3	11.11
Pneumococcus, Type III . . . . .	1	3.70
Organisms not identified . . . . .	3	11.10

PREVIOUS HISTORY OF PNEUMONIA. Previous history of pneumonia was found in 16 cases, or 11.67 per cent. Of these there were 4 cases that died, a percentage of 25.0 per cent.

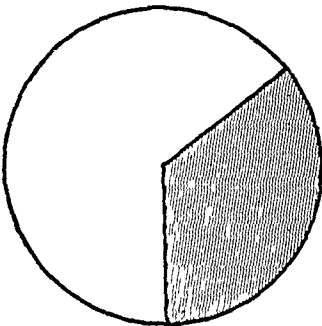
FIG. 11.



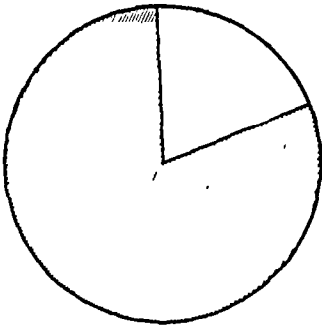
Previous history of pneumonia: Total number of cases, 137; previous history of pneumonia, 16; percentage, 11.67.



Death-rate in these cases: Total number of cases, 16; died, 4; percentage, 25.



Total of complications: Total number of cases, 137; cases with complications, 42; percentage, 30.65.

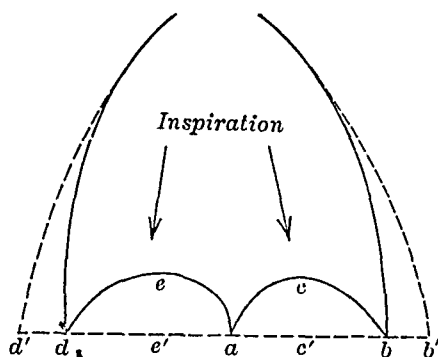


Total of effusions: Total number of cases with complications, 42; total, number of effusions, 33; percentage, 78.57.

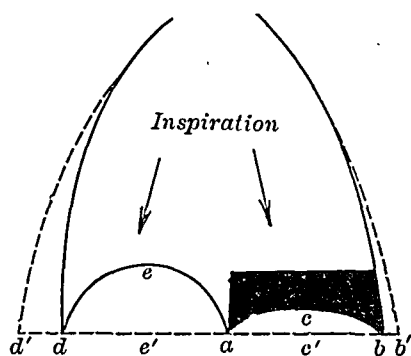
PLEURAL EFFUSIONS. In this series of 137 cases, pleural effusions were found in 33, or 24.08 per cent. Thus every fourth case was a case of effusion. This fact cannot be overemphasized.

Many of these cases of effusions have been aspirated a number of times. Our policy has been to do repeated aspirations as these were indicated, and when the empyemic process was walled off to resect the rib and drain the cavity.

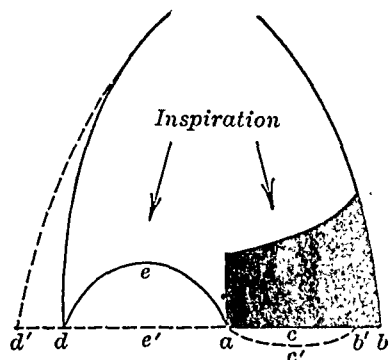
FIG. 12.—Hoover's sign.



Normal thorax. Notice the even flaring of the subcostal angles  $b-d$  on inspiration to  $b'-d'$  with the descent of the diaphragm from  $c-e$  to  $c'-e'$ .



Small amount of effusion. Notice the depressed diaphragm  $c$  on the side of effusion. With this the diminished excursion of the subcostal angle  $b$  to  $b'$  on inspiration while the other side has its normal excursion  $d$  to  $d'$ .



Large amount of effusion with depression of diaphragm to a straight line. Notice that on inspiration the subcostal angle  $b$  on the side of the effusion not only does not flare out but actually pulls in the distance between  $b$  and  $b'$ .

Such a high percentage of fluids goes to show that many effusions have accompanied the pneumonic process and that only a careful examination and an ever-present lookout for fluid will reveal this, as otherwise it will be passed by unnoticed.

What are the diagnostic points which are of aid to the physician in the diagnosis of fluids? I shall try to emphasize a few which may perhaps be of some help to others working in this field:

1. In the first place, taking a case with a typical pneumonia curve, after a crisis and the temperature staying normal for several

days, then suddenly beginning to rise in the evening of each day to 99.2, 99.6, etc., higher each day—look out for fluid.

2. With the dulness due to fluid the tactile fremitus is abolished unless the compression of the fluid is marked, in which case the fluid becomes a good conductor and will transmit the vibrations of the sound to the periphery. Experience and judgment alone count here.

3. Whispered voice sounds are well transmitted through fluid and have a characteristic quality which, once acquired, is easily recognized.

4. The last but not the least is the Hoover sign. This I tried to make clear in the accompanying diagram, exaggerating somewhat the true state of affairs for the sake of making my point clear. This to me has been many a time a very valuable diagnostic aid. You place your thumbs against the costal margins of the cartilages on the sub-sternal angle, the palm of the hand grasping the side of the chest as though one were trying to circumvene the lower part of the thoracic cage, the thumbs resting down about the junction of the eighth or ninth cartilage. You simply judge the distance of excursion of both sides of the chest during the inspiration, noticing whether or not there is any lagging of either side as compared with the other side. The side with the effusion will lag, due to the factors described in the diagrams.

#### LUNG PUNCTURES.

<i>Antemortem.</i>		Per cent.
1. Sterile . . . . .	8	40
2. Organisms . . . . .	12	60
Of these:		
(a) Streptococcus hemolyticus . . . . .	9	45
(b) Streptococcus viridans . . . . .	1	5
(c) Staphylococcus aureus . . . . .	1	5
(d) Organisms not identified . . . . .	1	5
(e) Sterile . . . . .	8	40
Total . . . . .	20	

<i>Postmortem.</i>		
1. Sterile . . . . .	2	40
2. Organisms . . . . .	3	60
Of these:		
(a) Pneumococcus, Type III . . . . .	1	20
(b) Streptococcus hemolyticus . . . . .	2	40
(c) Sterile . . . . .	2	40
Total . . . . .	5	

#### HEART PUNCTURES.

<i>Postmortem.</i>		
1. Sterile . . . . .	3	42.85
2. Organisms . . . . .	4	57.15
Of these:		
(a) Streptococcus hemolyticus . . . . .	3	75
(b) Pneumococcus, Type IV . . . . .	1	25

FIG. 13

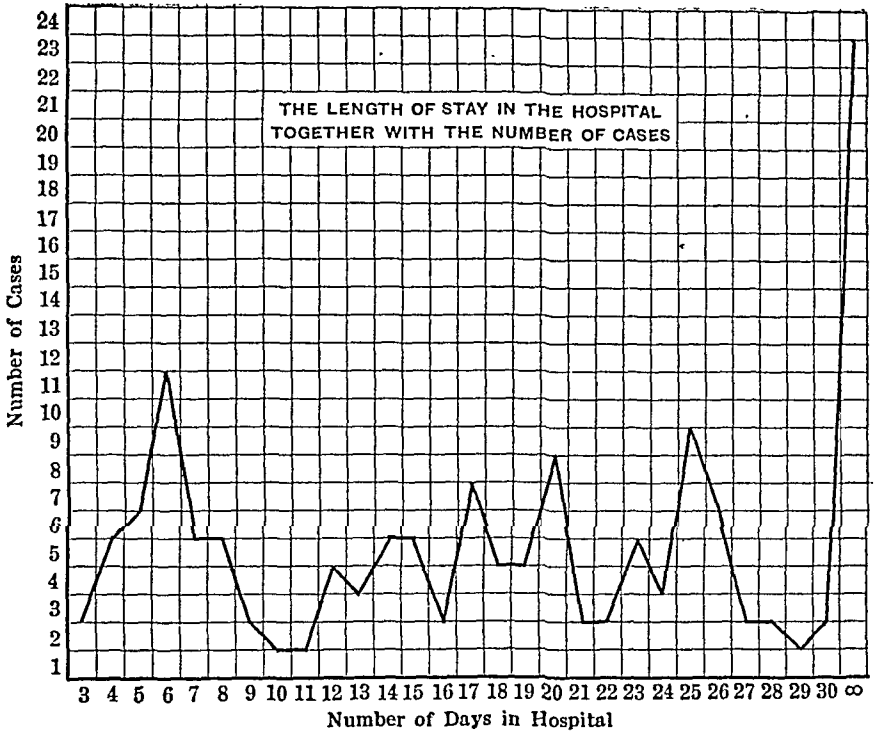
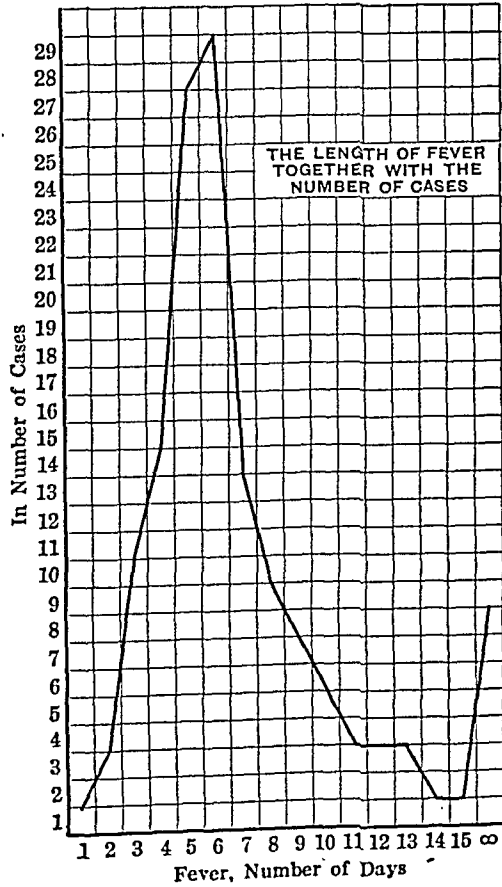


FIG. 14





## BLOOD CHEMISTRY IN PNEUMONIA

Name.	Date.	Per cent. of sugar.		Creatinine, mgm.	Uric acid, mgm.	Urea nitrogen, mgm.	Chlorides, per cent.	pH before glucose.	pH after glucose.	Rpm before glucose.	Rpm after glucose.
		Before glucose.	After glucose.								
McK.	Nov. 27	0.130	0.190	0.45	2.25	7.25	1.20				
R.	Nov. 28	0.146	0.269	0.75	2.95	11.50	0.49				
	Nov. 29	0.110	0.220	0.60	3.35	13.50	0.54				
M.	Nov. 29	0.104	..	0.75	..	17.75	0.50				
P.	Nov. 30	..	0.232	1.05	3.65	21.75	0.34				
M.	Nov. 29	0.096	0.750	..	3.65	22.75	0.50				
	Nov. 30	0.076	0.240	0.60	4.90	21.25	0.51				
	Dec. 1	0.110	0.194	0.45	1.28	20.00	0.49				
K.	Nov. 30	0.092	..	0.75	3.55	18.00	0.55				
S.	Dec. 2	0.098	0.190	0.70	3.65	16.25	0.47				
W.	Dec. 3	0.100	..	0.45	4.40	18.00	0.51				
	Dec. 4	0.108	0.252	0.45	..	16.75	0.57				
P.	Dec. 3	0.180	0.248	0.55	5.40	..	0.60				
P.	Dec. 3	0.070	0.400	0.40	4.70	19.50	0.50				
	Dec. 4	0.100	0.200	0.55	3.45	..	0.50				
A.	Dec. 5	0.160	0.232	..	..	..	..				
H.	Dec. 7	0.076	0.299	0.17	..	..	..				
R.	Dec. 10	0.100	0.204	1.10	..	16.75	..				
	Dec. 11	0.160	0.256	0.60	..	14.75	0.43	6.9			
	Dec. 12	0.180	0.204	..	..	16.75	0.43	7.6			
	Dec. 13	0.114	0.268	0.75	..	27.50	0.53	7.5	7.5		
B.	Dec. 9	..	0.204	0.60	..	..	..				
	Dec. 10	0.110	..	0.55	..	22.75	0.43				
	Dec. 11	0.104	0.264	0.45	..	13.00	..	..	7.4		
	Dec. 12	0.180	0.204	..	..	16.75	0.35	7.1	7.1		
T.	Dec. 9	0.128	0.228	1.00	..	..	..				
B.	Dec. 12	..	..	..	..	14.00	0.45	7.5			
McG.	Dec. 4	0.120	0.328	0.75	..	19.50	0.41	7.6	7.6		
	Dec. 16	0.160	0.216	0.60	..	..	0.50	7.4	7.4	7.5	7.5
K.	Dec. 22	..	0.132	..	..	..	..	..	7.4	..	7.9
R.	Dec. 23	..	..	..	..	..	..	7.4	..	7.4	
	Dec. 24	..	..	..	..	..	..	7.2	..	7.6	
W.	Dec. 31	..	..	..	..	..	..	7.5	7.5	8.5	8.5
	Jan. 1	..	..	..	..	..	..	7.4	7.2	8.0	7.8
G.	Jan. 1	..	..	..	..	..	..	7.6	7.5	7.8	7.3
	Jan. 2	..	..	..	..	..	..	..	7.5	..	7.8
R.	Jan. 10	..	..	..	..	..	..	7.5	7.3	8.4	8.2

CONCLUSIONS. 1. The incidence of *Streptococcus hemolyticus* in the throat has been high, viz., 42 per cent. Would prevention of this organism in the throat prevent the subsequent development of pneumonia?

2. More cases died with a negative blood culture than with a positive one. Here *Streptococcus hemolyticus* was the most frequently found organism in the blood stream.

3. Leukocytosis is undoubtedly a favorable factor in the prognosis.

4. History of a previous attack of pneumonia was found in 11.67 per cent. of the cases, of which 25 per cent. died.

5. Complications in this series of cases of pneumonia were present in 21.89 per cent.

6. Pleural effusions were found in 24.08 per cent. of the cases.

# A FURTHER STUDY OF THE RELATION OF HOUSING TO PULMONARY TUBERCULOSIS. REPORT ON 18,891 CASES.<sup>1</sup>

BY FRANK F. D. RECKORD, M.D.,

HARRISBURG, PA.

IN November, 1918, the author reported a study of the "Relation of Housing to Pulmonary Tuberculosis, with a Report on 36,062 Cases."<sup>2</sup> The subject is of great importance at this time, and there has been little written upon it in this country. As the author has had numbers of requests to continue his researches, it has been deemed advisable to publish the results in another series of 18,891 cases. In the first report it was emphasized that, if the houses of the poor are improved, the morals to an important extent will be improved, and in so doing the health and the relative efficiency will be benefited.

We must profit by the example of other nations and be inspired to make possible the pursuit of happiness for our huge army of struggling toilers. We must recognize the need as an economic rather than a philanthropic one; we must appreciate the ineffectiveness of our elaborate school systems in making good citizens when the influence of the home is opposed to it; we must recognize the evils incident to bad housing. We must also keep sound and strong the large foreign element which is being constantly woven into our social fabric. Their foreign ideals must be raised to American standards of citizenship, and that cannot be done under the present housing conditions of the poor and dependent, which obtain now in most districts to which they are generally drawn.

So long as there is no specific cure for tuberculosis we have no means of combating the disease except by adjusting environment, increasing the power of resistance and producing conditions favorable to the prevention and cure of the disease. There can be no doubt that fresh air, proper feeding, cleanliness of person and surroundings, rest, tranquillity of mind, careful regulation of the habits of the patient and regulated exercise are the factors on which a cure is based. They may therefore be considered as remedies. So long as there is poverty, with all its accompaniments, bad housing, insufficient nourishment, unsanitary conditions of industry, ignorance and many other evils undermining the welfare of society there will be tuberculosis, with the usual results of suffering, deterioration and premature death. The hope for better days lies not only in the prevention of the disease but in the eradication of the causes and the existing conditions that influence the spread of tuberculosis.

<sup>1</sup> Received for publication February 6, 1920. Read before the Harrisburg Academy of Medicine, February 27, 1920.

<sup>2</sup> Reckord, Frank F. D.: AM. JOUR. MED. SC., November, 1918, No. 5, clvi, 670.

As the evils of housing are so largely corrected by educational methods, we cannot hope to correct them without the assistance of all educational factors. We are beginning to do what should have been undertaken a long time ago, to impress upon the youth while in school the essential lessons of right living.

Children are susceptible very early in life to public health education, and if the elementary foundations of sanitary consciences are well laid in the schools, these pupils, when fully grown, will be the sanitary educators of the next generation.

In the study of these cases the 18,891 cases have been divided into two groups, of 10,340 and 8551 respectively:

In the former series:

247 families had	1 member, representing	247 members.
681 "	2 members, "	1362 "
1288 "	3 " "	3864 "
1565 "	4 " "	6260 "
1624 "	5 " "	8120 "
1437 "	6 " "	8622 "
1034 "	7 " "	7238 "
774 "	8 " "	6192 "
738 "	9 " "	6642 "
122 "	10 " "	1220 "
83 "	11 " "	913 "
32 "	12 " "	384 "
18 "	13 " "	234 "
15 "	14 " "	210 "
7 "	15 " "	105 "
5 "	16 " "	80 "
6 "	18 " "	108 "
1 "	19 " "	19 "
1 "	21 " "	21 "
1 "	30 " "	30 "

661 families, members not stated.

Thus the sum total, not including the 661 families where members were not stated, represents 9679-families and 51,871 members, or an average number of persons to one family of 5.4 members.

In the second series, comprising 8551 cases:

194 families had	1 member, representing	194 members.
527 "	2 members, "	1054 "
988 "	3 " "	2964 "
1286 "	4 " "	5144 "
1370 "	5 " "	6850 "
1210 "	6 " "	7260 "
899 "	7 " "	6293 "
650 "	8 " "	5200 "
649 "	9 " "	5841 "
66 "	10 " "	660 "
35 "	11 " "	385 "
32 "	12 " "	384 "
15 "	13 " "	195 "
25 "	14 " "	350 "
12 "	15 " "	180 "
3 "	16 " "	48 "
2 "	17 " "	34 "
3 "	18 " "	54 "
1 "	19 " "	19 "
5 "	20 " "	100 "
1 "	24 " "	24 "
1 "	27 " "	27 "
2 "	40 " "	80 "

575 families, members not stated.

Thus the sum total, not including the 575 families where members were not stated, represents 7976 families and 43,340 members, or an average number of persons to one family of 5.4 members.

In the group of 36,062 cases previously reported the average number of persons to a family was 5.2 members.

The number of rooms per family is an important study. Considering this problem in the first series of cases.

985 families occupied			1 room, representing	985 rooms.
2674	"	"	2 rooms,	" 5348 "
3523	"	"	3 "	" 10569 "
1523	"	"	4 "	" 6092 "
519	"	"	5 "	" 2595 "
200	"	"	6 "	" 1200 "
48	"	"	7 "	" 336 "
23	"	"	8 "	" 184 "
12	"	"	9 "	" 108 "
0	"	"	10 "	" 0 "
3	"	"	11 "	" 33 "
1 family	"	"	14 "	" 14 "

829 families occupied rooms, number not stated.

The sum total of families, not including those in which the number of rooms was not stated, is 9511 and the number of rooms amounts to 27,464; making an average number of 2.8 rooms per family.

In the second series:

743 families occupied			1 room, representing	743 rooms.
2099	"	"	2 rooms,	" 4198 "
3021	"	"	3 "	" 9063 "
1237	"	"	4 "	" 4948 "
463	"	"	5 "	" 2315 "
165	"	"	6 "	" 990 "
38	"	"	7 "	" 266 "
18	"	"	8 "	" 144 "
13	"	"	9 "	" 117 "
2	"	"	10 "	" 20 "
2	"	"	11 "	" 22 "
1	"	"	12 "	" 12 "
1	"	"	13 "	" 13 "
2	"	"	15 "	" 30 "
2	"	"	18 "	" 36 "
1	"	"	25 "	" 25 "

743 families occupied rooms, number not stated.

The sum total of families, not including the 743 in which the number of rooms was not stated, is 7808, and the number of rooms amounts to 22,942, making an average number of 2.9 rooms per family.

In the 36,062 cases reported the number of rooms amounted to 102,674, or an average number of 2.8 per family. So the average number of rooms per family may safely be taken as 2.8 per cent.

In this connection it is next important to know the number of persons in the family compared with the number of rooms occupied.

In the first group it was found that:

224	cases	having	1	member	to a family	occupied	1	room.
242	"	"	2	members	"	"	1	"
214	"	"	3	"	"	"	1	"
133	"	"	4	"	"	"	1	"
89	"	"	5	"	"	"	1	"
33	"	"	6	"	"	"	1	"
23	"	"	7	"	"	"	1	"
15	"	"	8	"	"	"	1	"
12	"	"	9	and over				

Total, 985 cases, having from 1 up to 9 members and over occupied 1 room.

Just as interesting are the data concerning the number of people that lived in 2 rooms:

9	families	having	1	member	to a family	occupied	2	rooms.
242	"	"	2	members	"	"	2	"
478	"	"	3	"	"	"	2	"
568	"	"	4	"	"	"	2	"
476	"	"	5	"	"	"	2	"
385	"	"	6	"	"	"	2	"
224	"	"	7	"	"	"	2	"
162	"	"	8	"	"	"	2	"
119	"	"	9	and over	"	"	2	"

Total, 2663 families, having from 1 up to 9 members and over, occupied 2 rooms.

Continuing the study I find that 3519 families made up of 1 to 9 members and over, abode in 3 rooms as follows:

4	families	having	1	member	to a family	occupied	3	rooms.
130	"	"	2	members	"	"	3	"
414	"	"	3	"	"	"	3	"
570	"	"	4	"	"	"	3	"
676	"	"	5	"	"	"	3	"
630	"	"	6	"	"	"	3	"
431	"	"	7	"	"	"	3	"
284	"	"	8	"	"	"	3	"
380	"	"	9	and over	"	"	3	"

From the above information it will be noted that 7167 families out of the total 9511 under consideration in the group of 1 up to 9 and over membership, or 75.3 per cent., occupied from 1 to 3 rooms. In the study of 36,062 the percentage of those living in 1 to 3 rooms was 74.5 per cent., thus showing a marked similarity.

Of the remaining 2344 families, 1523, or 16 per cent., composed of the same number of members as given, occupied 4 rooms, while 826, or 8.7 per cent., lived in 5 rooms and over.

From this compilation of figures this interesting and striking summary is obtained:

Total number of rooms occupied by families of 9511 patients, the number of whose rooms is given . . . . .	27,464 rooms
Membership of families of 9679 patients, 5.4 members to the family . . . . .	51,871 persons
Average number of persons to each room . . . . .	1.9 "
Average number of rooms to each family, 5.4 members . . . . .	2.8 rooms.

TABLE I.—SOCIAL STATISTICS CONCERNING THE 10,340 CASES OF PULMONARY TUBERCULOSIS. TABLE SHOWING NUMBER OF PERSONS COMPARED WITH NUMBER OF ROOMS OCCUPIED.

Occupants:	Total.	Rooms.					
		1	2	3	4	5 and over	Unstated.
Total	10340	985	2674	3523	1523	806	829
Unstated	661	0	11	4	2	8	636
1 . . .	247	224	9	4	1	0	9
2 . . .	681	242	242	130	26	9	32
3 . . .	1268	214	478	414	104	43	35
4 . . .	1565	133	568	570	189	73	32
5 . . .	1624	89	476	676	267	88	28
6 . . .	1437	33	385	630	253	110	26
7 . . .	1054	23	224	431	221	119	16
8 . . .	774	15	162	284	193	114	6
9 and over	1029	12	119	380	267	242	9

Total number of rooms occupied by families of 9511 patients the number of whose rooms is given . . . 27,460 rooms

Membership of families of 9679 patients, 5.4 members to the family . . . 51,871 persons

Average number of persons to each room . . . 1.9 "

Average number of rooms to each family of 5.4 members . . . 2.8 rooms

Taking up the same problem of number of persons in family compared with the number of rooms occupied, in the second group of 8551 cases, which has been carried out much further than the preceding data, following a suggestion by Dr. Raymond Pearl, of the Johns Hopkins University, of Baltimore, we find that:

164 cases having	1 member	to a family occupied	1 room.
195	"	"	2 members
149	"	"	3
97	"	"	4
57	"	"	5
46	"	"	6
22	"	"	7
6	"	"	8
2	"	"	9
2	"	"	11
1	"	"	12

Total, 741 families, composed of 1 up to 12 members occupied 1 room.

There were 2095 families, composed of 1 to 14 members quartered in 2 rooms as follows:

4 families having	1 member	to a family occupied	2 rooms.
178	"	"	2 members
351	"	"	3
429	"	"	4
375	"	"	5
320	"	"	6
228	"	"	7
120	"	"	8
73	"	"	9
7	"	"	10
7	"	"	11
2	"	"	12
2	"	"	13
1	"	"	14

More astonishing is the information relative to those who lived in 3 rooms:

6 families having		1 member to a family occupied 3 rooms.	
79	"	2 members	"
353	"	3	"
498	"	4	"
616	"	5	"
484	"	6	"
348	"	7	"
311	"	8	"
278	"	9	"
14	"	10	"
7	"	11	"
6	"	12	"
5	"	13	"
3	"	14	"
1	"	15	"
1	"	18	"
1	"	19	"
1	"	40	"

Total, 3012 families, made up from 1 to 40 members, occupied 3 rooms.

From this information it will be noted that of this series of 8551 cases, of which 743 gave no data as to rooms occupied (thus leaving 7808), there were 5848 families of 1 up to 40 membership, or 74.8 per cent. that occupied 1 to 3 rooms.

Of the remaining 2060 families, 1234, or 15.6 per cent., composed of 1 to 27 members, occupied 4 rooms, while 826 families, or 10.5 lived in 5 up to 25 rooms.

From this compilation of figures this interesting summary is obtained:

Total number of rooms occupied by families of 7808 patients, the number of whose rooms is given . . . . .	22,942 rooms
Membership of families of 7976 patients, 5.4 members to the family . . . . .	43,340 persons
Average number of persons to each room . . . . .	1.9 "
Average number of rooms to each family of 5.4 members	2.9 rooms

The author believes that the above study will be convincing and that the figures as to the average number of members to a family, the number of persons to a room and the average number of rooms to a family may be taken as a unit of comparison, as there is a marked similarity in the three series amounting to 54,953 cases.

Not only should the home conditions be carefully studied, but also the effect of occupational environment. The contributory factors in the development of tuberculosis in those employed in the industries are no different in kind from those outside the workshop. The only difference is in degree. When in an industry some factor is intensified, or there is a combination of factors, we say there is an occupational hazard.

Tuberculosis following a long period of exposure to injurious conditions is by far the most common history in all but a small

number of cases in which the hazards of occupation play an important part.

TABLE II.—SOCIAL STATISTICS CONCERNING THE 8551 CASES OF PULMONARY TUBERCULOSIS. TABLE SHOWING NUMBER OF PERSONS COMPARED WITH NUMBER OF ROOMS OCCUPIED.

	Total	Rooms.																		
Occu- pants.		1	2	3	4	5	6	7	8	9	10	11	12	13	15	18	25	Unstated.		
Total	8551	743	2099	3021	1237	463	165	38	18	13	2	2	1	1	2	2	1	743		
Unstated	575	2	4	9	3	0	5	0	1	1	0	0	0	0	0	0	0	550		
1	194	164	4	6	1	1	0	0	0	0	0	0	0	0	0	0	0	18		
2	527	195	178	79	30	6	2	1	0	0	0	0	0	0	0	0	0	36		
3	988	149	351	353	82	24	5	2	0	0	0	0	0	0	0	0	0	22		
4	1286	97	429	498	162	53	7	3	3	0	0	0	0	0	0	0	0	34		
5	1370	57	373	616	203	75	16	5	0	1	0	0	0	0	0	0	0	24		
6	1210	46	320	484	231	65	31	8	0	1	0	0	0	0	0	0	0	24		
7	899	22	228	348	178	72	27	2	1	1	1	0	0	0	0	0	0	19		
8	650	6	120	311	120	52	22	3	3	1	0	1	0	0	0	0	0	11		
9	649	2	73	278	184	70	30	3	2	4	0	0	0	0	0	0	0	3		
10	66	0	7	14	14	12	8	4	4	1	1	0	0	0	0	0	0	1		
11	35	2	7	7	8	5	2	0	1	2	0	1	0	0	0	0	0	0		
12	32	1	2	6	9	5	3	3	2	0	0	0	0	0	0	1	0	0		
13	15	0	2	5	4	2	1	1	0	0	0	0	0	0	0	0	0	0		
14	25	0	1	3	2	14	1	2	0	1	0	0	0	0	0	1	0	0		
15	12	0	0	1	2	5	3	0	0	0	0	0	0	0	0	0	1	0		
16	3	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0		
17	2	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0		
18	3	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0		
19	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
20	5	0	0	0	0	0	0	0	1	0	0	0	1	1	0	1	0	1		
24	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0		
27	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0		
40	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0		

Total number rooms occupied by families of 7808 patients, the number of whose rooms is given

Membership of families of 7976 patients, 57.4 members to the family

Average number of persons to each room

Average number of rooms to each family of 5.4 members

22,942 rooms  
43,340 persons  
1.9 "  
2.9 rooms

One of the most harmful factors is dust; dusts may be divided according to their physical character as follows:

(a) Cutting dusts, formed of minute, hard, crystallized particles which have sharp, cutting and pointed edges. These dusts are composed of iron, or steel, of stone, of sand, or glass, of dried silicates in earthenware, of lime, of pearl.

(b) Irritant dusts, derived from woods, from ivory, from textile fabrics, fluffs of wool, of silk, of cotton, of flax and of hemp, from hair, from clay.

(c) Inorganic poisonous dusts, derived from some poisonous chemical compound used for coloring artistic products or for preserving organic substances, such as furs. These dusts are charged with arsenical salts.

(d) Soluble saline dusts, derived from soluble crystallized substances used for dyeing purposes; sulphate of iron and copperas yield dusts of this class.



(e) Organic poisonous dusts, which are thrown off during the making up of tobacco into cigars and snuff. These dusts carry with them particles of the dried tobacco plant.

(f) Obstructive and irritating dusts composed of carbon, of fine particles of coal dust, of scrapings of carbon or of soot, of rouge and of flour.

Most of the recent studies on inorganic dust are convincing that metallic and siliceous dusts are the most potent causes of pulmonary fibrosis. The latter is most important because more frequently encountered. The second report of the British Royal Commission on Metalliferous Mines and Quarries (1914) quote experiments of Beattie as follows:

"Certain mineral dusts, such as coal, clay, cement, were not shown by experiment to be injurious. Other dusts, *e. g.*, silica, quartz, flint, sandstone, are injurious, as are also carborundum and emery. After careful consideration, therefore, we feel justified in concluding that, even although further investigation should disclose other dusts as injurious, the dust of fine crystalline silica is especially injurious and is more potent cause of fibrosis."

The commission was further of the opinion that inorganic dusts may be grouped in two classes:

1. "Dusts, the inhalation of which has not so far been shown to be associated with any marked increased mortality from respiratory diseases, to this class belong coal, steel, slate, iron ore, clay, limestone, plaster of Paris and cement." (2) "Dusts, the inhalation of which is associated with excessive mortality from respiratory diseases, and especially from phthisis, to this class belong quartz, quartzite (*i. e.*, ganister and buhr stone), flint and sandstone."

The hard, gritty dust composed of sharp and jagged particles are the ones to be especially feared. The least important of the inorganic dusts is soot. The grinding trade includes a large variety of employments, of which metal grinding by either the dry or wet process is hygienically as well as industrially the most important. The grinding of metal probably involves as much exposure to decidedly health-injurious conditions as does any other employment, if not more so. Chiefly as the result of the inhalation of relatively large quantities of fine metallic dust, and not inconsiderable quantities of fine mineral dust, the mortality from pulmonary tuberculosis in this occupation is decidedly above the normal for occupied males generally. The size of the individual particles plays an important part. The finer the dust, the more dangerous, as it is only the very finest particles which gain access to the lungs. According to Oliver, so far as the two methods of grinding cutlery are concerned, the dry method is, from a health point of view, the more dangerous to the workers. The dust is dry and is in the form of a very fine powder, which readily reaches the lungs owing to the attitude of the men when at work. Steel grinders sit astride the

grinding stone on a saddle, and as they lean forward keeping close to their work, they cannot but inhale some of the dust, which is a mixture of steel and stone. Forks and needles are generally ground by the dry method; knives, scissors, and razors by the wet method. Some are ground by both methods, *e. g.*, the backs of razors and scissors are ground by the dry method and the remainder of the blade by the wet. It was in 1865 that Dr. T. C. Hall, of Sheffield, drew attention to the high death-rate of steel grinders from pulmonary tuberculosis. The average age at death of steel grinders was at this period only twenty-nine years, but of late this has improved. His statistics referred to dry grinding. In wet grinding the running stone passes through a thin layer of water in a trough below the stone, so that, as its surface is always kept wet, comparatively little dust is given off during the process of grinding; but while the atmosphere is clearer of dust the floors and walls of the workshop are damp and cold. It is no uncommon thing to find men engaged in different processes in one large room, so that the dust that is generated affects not only the workman sitting at his own grinding stone but the other inmates of the room as well.

In the case of a worker exposed to unusual quantities of inorganic dust the majority of the particles are, for a varying length of time, arrested by the moist surface of the mucous membrane, by the action of the ciliated epithelium and by the phagocytes. Sooner or later these defensive forces weaken and finally the dust passes into the lymph channels and also along the finer bronchi until it reaches the parenchyma of the lungs. As a foreign substance it then sets up a chronic inflammatory process.

The experience of Landis,<sup>3</sup> Arlidge<sup>4</sup> and others is that the anterior and inferior marginal portions of the lungs, where expansion is most free, are always less affected than the posterior and apical portions. Radiographic evidence shows also that change frequently is slightly more advanced in the right lung than in the left.

The observation of a British departmental committee upon respiratory diseases, and in particular bronchitis, pneumonia and tuberculosis and their relation to occupation exposure, were that "pulmonary disease manifests itself in three kinds or forms: as ordinary tuberculous phthisis, acute or chronic; as fibroid phthisis, and as a mixed form when a tuberculous process is ingrafted sooner or later upon the fibroid. Fibroid phthisis is always a slow disease. It consists in a chronic reactive inflammation around the many minute foci of dust inhalation, which by coalescence gradually invades large areas, impairing and strangling the proper lung tissues in corresponding measure. Again a lung so impaired is very liable to harbor bacilli, especially the tubercle bacilli, by the influence of

<sup>3</sup> Landis, H. R.: Jour. Indus. Hyg., July, 1919, No 3, i, 117-139.

<sup>4</sup> Arlidge, J. T.: Hygiene-Diseases and Mortality of Occupation, London, 1892, p. 251.

which it may be still further destroyed." Frequently it is most difficult to determine whether the condition is tuberculous or not, and even the roentgenograms may be difficult to interpret. Patients are frequently admitted to sanatoria with a diagnosis of pulmonary tuberculosis, but what they are really suffering from is a diffuse fibrosis of the lungs and dilatation of the bronchi.

Another thing that cannot be emphasized too strongly is the evident difference in resistance of individuals to dust. Two men may be working at the same occupation and under the same environment, and yet one will show marked fibrosis and the other may show little change.

From the bacteriological studies of Sweaney and MacLane<sup>5</sup> in testing samples of dust it was found that of 134 samples taken from rooms where open cases of tuberculosis were being treated 12 were positive. Of 18 samples taken from a county jail 3 were positive. Seven positive samples were found in single and double rooms facing north while only two were found in rooms facing south. The greatest percentage of positive samples were found in places where the greatest number of open cases were being treated. It may thus be readily appreciated what a menace dust is, generally as it is such a convenient carrier of the tubercle bacilli.

The factor of ventilation is relative; the more dust the more ventilation required. It is just as important that men, women and children receive proper ventilation during the day as at night. A small amount of dust or fumes may be very dangerous if there is no provision for fresh air. Overcrowding in a work room is a menace. Excessive humidity coupled with extremes of heat or cold tend to reduce bodily resistance; and this makes another hazard for the workman.

Along with exposure to dust and improper ventilation, overcrowding, the posture of the workman, nervous strain and the fatigue of too swift a pace or too long hours are some of the more important factors to be considered in connection with the effect of occupational environment.

In the 10,340 cases of our first series there were 5815 males and 4525 females. From the occupational standpoint the males under occupational age totaled 805 (native 768, foreign 36, unstated 1); those with no occupation, 1707 (native 1023, foreign 684); those occupied 3303 (native 1972, foreign 1331); grand total 5815.

Studying those occupied it was found that the engineers and surveyors led the professional group; book-keepers, clerks, and copyists maintain their usual lead in the clerical and official group, commercial travelers in the mercantile and trading group, saloon-keepers and bartenders in the public service group and barbers and hair-dressers in the personal service group. The foreign laborers

<sup>5</sup> Sweaney and MacLane: Illinois Med. Jour., 1919, No. 6, xxxix, 302.

outnumber the native in the laboring and servant group. In the manufacturing and mechanical industry group the machinists come first with the steel-workers, tailors, mill and factory operatives (textile), carpenters and joiners, stationary engineers and firemen, clock and watch repairers, jewelers, boot and shoemakers, painters and glaziers, plumbers, gas and steam fitters, blacksmiths, butchers, cigarmakers and tobacco workers following in order named.

In the agricultural and transportation group the miners and quarrymen come first, followed by draymen, hackmen, teamsters, steam railroad employees and farmers, planters and farm laborers. The laboring and manufacturing groups lead with the largest numbers respectively.

In regard to the female occupations the housewife predominates, followed in the gainful occupation class by servants, mill and factory operatives, bookkeepers, clerks, copyists, dressmakers, seamstresses, laundresses, stenographers and typewriters in order named. Those under occupational age numbered 926 (native 883, foreign 43); those with no occupation 944 (native 778, foreign 166); all occupations total 2655 (native 1884, foreign 771).

In the second series of 8551 cases there were 752 native, 29 foreign and 1 unknown males who were under occupational age. Under the heading of no occupation appears 1000 native and 609 foreign, 4 unknown. In the group of occupations 1444 were native, 995 foreign and 6 unknown. Of the 796 females under occupational age 760 were natives, 36 foreign; there were 765 with no occupation (645 native, 120 foreign); those occupied were 2147, with 1521 native and 623 foreign, 3 unknown.

Of those occupied there is a similarity in findings, but in the personal service group it is interesting to note that next to the barbers and hair-dressers follow closely the soldiers, sailors and marines and not far behind the policemen, watchmen and detectives.

The Pennsylvania State Department of Health has a model housing ordinance for cities and boroughs to follow in enacting ordinances.

1. It shall be the duty of the board of health to investigate the sanitary conditions of tenement, rooming, lodging and boarding houses, and when the same are found not to be in conformity with the requirements of this ordinance, or in the opinion of the board of health to be a menace to those occupying the same, or employed therein, or to be overcrowded, to condemn the same and to notify the owners or agents thereof in writing, setting forth the non-compliance with requirements of this ordinance, or the insanitary or overcrowded conditions thereof and specifying in writing the changes or alterations which shall be made thereto for the purpose of relieving such conditions and further specifying the time within which such changes or alterations shall be completed or overcrowding relieved.

2. For the purpose of this ordinance the several classes of buildings referred to herein are defined as follows:

(a) A lodging house shall mean any building or portion thereof in which five or more persons are furnished with sleeping accommodations for a single night either for hire or for charity.

(b) A rooming house shall mean any building or barracks or portion thereof in which persons are received, housed or lodged either for hire or for charity.

(c) A boarding house shall mean any building or portion thereof in which persons are received, housed, lodged or furnished with meals for hire.

(d) A tenement shall mean any building or portion of a building or block of buildings which is occupied by two or more families who have a common right in the halls, stairways, cellars and plumbing, yard or any one of them. Tenements shall include apartment houses apartment hotels, flats, two- and three-family houses, and any building not otherwise described which is used for multiple habitation where any portion thereof is used in common.

3. All buildings of the classes specified herein located on or adjacent to a highway in which a public water main is laid shall have the public water supply distributed through the building as to furnish an adequate quantity of wholesome water, with reasonable facilities for drinking and washing purposes for the occupants thereof; provided, that in tenements each family shall be furnished with water supply for their separate use. All buildings of the classes specified herein so located that a public water supply is not accessible, shall be furnished with an approved private water supply distributed in an approved manner.

4. All buildings of the classes specified herein located on or adjacent to a highway in which a public sewer is laid shall have the drainage system of the building connected thereto, and there shall be furnished adequate and sanitary toilet facilities for separate use of each family. All buildings of the classes specified herein so located that a public sewer is not accessible shall be furnished with a substantial and sanitary type of cesspool, privy or other device, constructed, installed and maintained in an approved manner; provided, that in tenements each family shall have separate toilet facilities.

5. All rooms used for sleeping purposes in buildings of the classes specified herein shall have at least 600 cubic feet of air space or 70 square feet of floor area for each occupant of said room; provided, that no cellar, basement, lower story or any portion of a building of which one-half of the height from the floor to the ceiling is below the level of the ground adjoining, shall be used for sleeping purposes.

6. All buildings of the classes specified herein shall be so located that reasonable open space or spaces furnishes natural light and air to the windows of each room in said buildings. Each room in said buildings used for living or sleeping purposes shall have a window

or windows opening directly to the outside and furnished with sash so constructed and maintained that they may be easily opened to provide ample ventilation. Said windows shall be proportioned as follows:

#### MINIMUM AREA OF WINDOWS.

Number of persons occupying room.	Window area in square feet per capita.	
	When window is in one wall.	When windows are in opposite walls.
1 . . . . .	10	8.0
2 . . . . .	9	7.0
3 . . . . .	8	6.5
4 or more . . . . .	7	6.0

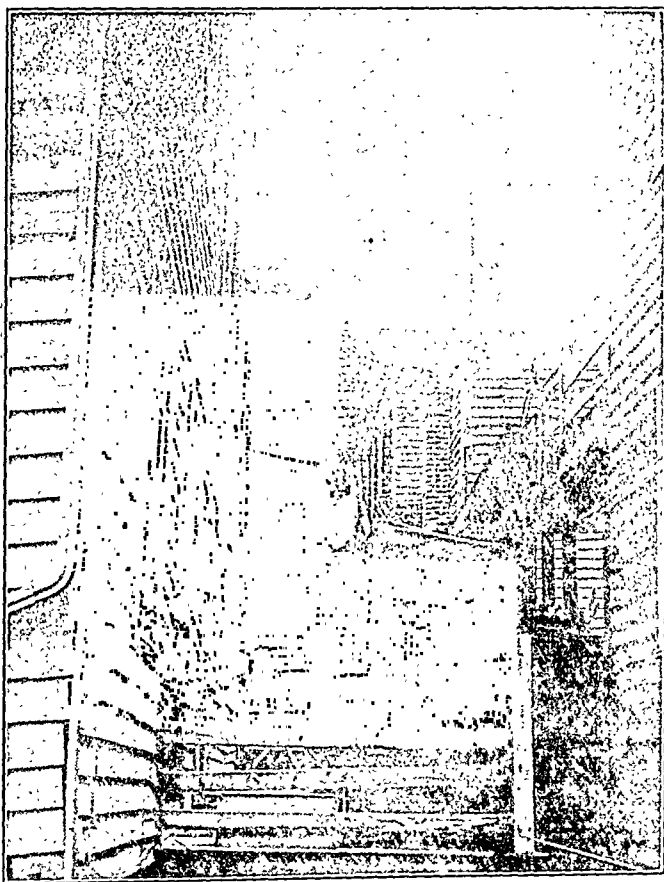


FIG. 1.—Extreme overcrowding of land.

7. Any building of the classes specified herein or any portion thereof shall not be occupied if it is in such condition, that in the judgment of the board of health sanitary methods of living cannot be maintained. If the board of health deems it necessary in the interest of the public health they shall notify in writing the owner or agent of any such building describing the insanitary conditions that exist therein requiring the same to be abated within a specified

time and that after the expiration of the time specified the premises shall not be occupied unless they be placed in an approved sanitary condition. If at the expiration of the time given in the said notice its requirements have not been complied with, the said building shall be vacated and the board of health shall post a sign or placard upon the property in a conspicuous place, stating that the building or any part of it, or the premises, as the case may be, is in an insanitary condition and shall not be occupied.



FIG. 2.—Filthy alley—no place for children to play.

8. Whenever notice is given under the provisions of this ordinance, the same shall be served upon the person to make such correction, or his agent, by the duly authorized agent of the board of health, or by mailing a copy of the said notice to the last known address of such person or his agent, and by posting a copy of this notice in a conspicuous place upon the premises affected. The notice and placard or sign stipulated in Paragraph 7 hereof shall not be removed or defaced until its removal is authorized in writing by the board of health.

9. Any person, firm or corporation who shall violate any of the provisions of this ordinance shall upon conviction before any justice

of the peace, alderman or magistrate be fined not less than five (\$5) dollars per day or more than twenty-five (\$25) dollars per day, for each day during which the premises have been used after the expiration of the time specified in the aforesaid notice of the board of health and also the cost of prosecution.

10. In case any violation of this ordinance also constitutes a violation of an Act of Assembly of Pennsylvania for which a penalty is provided by law, with which penalty the penalty provided by

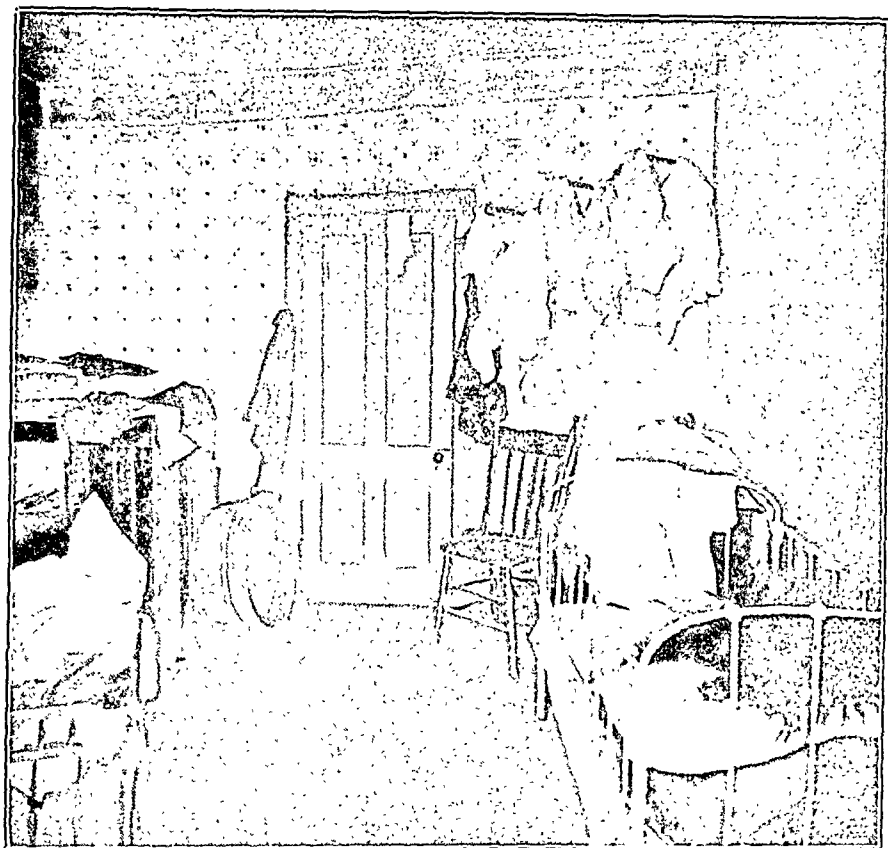


FIG. 3.—Windowless room—occupied by three small children.

this ordinance may be inconsistent, in such cases the penalty provided by the Act of Assembly shall take precedence and shall be the penalty imposed for such violation.

11. Whenever in this ordinance the words 'accessible, approved, reasonable, available' or words of like import are used, it shall be understood that the accessibility, approval, reasonableness, availability shall be determined by the Board of Health.

12. All ordinances or parts of ordinances inconsistent herewith are hereby repealed.

**Appendix.** Housing improvements are primarily directed to the structural features of the building; however, it must be borne in



mind that other factors enter into the problem and it may be advisable to add sections to the ordinance covering the following points:

(a) That no buildings of the classes specified herein shall be constructed on the rear end of a lot or in conjunction with other buildings unless the said building shall have a full frontage upon a public street and be so located that the said building shall not cut off or interfere with the light and air of any building on the same lot.

(b) That no tenement house or lodging house hereafter erected may be occupied where a public sewer is not accessible or where the public street is not sewered, graded and open to public travel.



FIG. 4.—The above picture shows that even in semirural districts, where there would seem to be sufficient sunlight and fresh air for all, conditions exist which practically duplicate the worst overcrowding of our cities.

It must further be borne in mind that the cleanliness of the building and its environments are essential to wholesome living conditions, for example:

(c) In tenement houses the owner should be held responsible for the maintenance of the common halls, stairways, cellar, yard, etc., in a cleanly condition.

(d) The accumulation of rubbish, ashes, garbage or organic wastes on the premises of tenement houses shall not be permitted.

(e) The grounds of tenement houses and lodging houses shall be either paved or graded and drained so that water will not be retained.

These items (c) (d) (e) may be controlled by adding proper sections to this ordinance or by considering such conditions as public nuisances and the board of health abating them as such.

TABLE III.—CHARACTER OF DWELLINGS OCCUPIED BY 14,365 CASES OF PULMONARY TUBERCULOSIS AND ALLIED CONDITIONS.

Classification.	Sex.	Total.	Private house.	Apartment.	Tenement.	Boarding house.	Institution.	Army camp.	Shanty.	Stable.	Unstated.
		14,365	11,964	864	801	227	415	3	3	2	86
Incipient . . . . .	M.	1,688	1,452	81	95	21	34	0	0	0	5
	F.	1,669	1,490	77	61	7	32	0	0	0	2
Moderately advanced	M.	3,833	3,076	259	250	93	115	1	3	2	34
	F.	2,628	2,255	167	129	17	46	0	0	0	14
Far advanced . . . . .	M.	2,869	2,272	188	174	77	146	2	0	0	10
	F.	1,417	1,222	87	47	12	38	0	0	0	11
Glands . . . . .	M.	114	85	2	19	0	2	0	0	0	6
	F.	131	104	1	20	0	2	0	0	0	4
Other tuberculosis . . . . .	M.	6	4	1	1	0	0	0	0	0	0
	F.	10	4	1	5	0	0	0	0	0	0

From the above table it will be noted that 11,964 cases, or 83 per cent. lived in private houses. Of course, these houses differ greatly as to the number and size of rooms. We should consider the construction and location of the average private house in the poorer section of our cities—frequently long rows of small, dark houses opening upon courts, thus being deprived of the sunlight and dresh air, and kept in poor repair, subject to damp or wet cellars, poor sanitation, incubators for infections, such as tuberculosis. When it is realized that between 74 and 75 per cent. of families, averaging 5.4 members to a family live in 1 to 3 rooms, it is readily seen how difficult it is to arrange for the management of a tuberculous member and the need of sanatorium treatment in such instances is obvious.

Of these 14,365 cases, 3357 were classified in the incipient stage: 1688 males and 1669 females respectively.

In the moderately advanced stage there were 3833 males and 2628 females, or a total of 6461. The males outnumber the females by 1205.

In the far-advanced class there were 2869 males and 1417 females, or a total of 4286. Here also the males predominated by 1452.

The reason for the preponderance of the males is obvious and has been elaborated upon in the preceding report.

The death-rate from pulmonary tuberculosis in the registration area of the United States for 1917 was 128.9 per 100,000 or a total of 97,047 deaths. In the commonwealth of Pennsylvania the death-rate per 100,000 in 1918 was 128.4, or a total of 11,298 deaths. Investigating the matter in some of the well-known cities of Pennsylvania we find:

Estimated population of a number of cities in Pennsylvania and deaths from pulmonary tuberculosis during 1918. Foreign and negro element of population expressed in percentage.

Cities.	Population.	Foreign, per cent.	Negro, per cent.	Deaths.
Allentown . . . .	66,708	12.0	0	88
Altoona . . . .	60,757	10.0	..	29
Bethlehem . . . .	14,554	6.2	0	13
Bradford . . . .	15,789	15.0	0	10
Butler . . . .	29,670	17.0	0	22
Carbondale . . . .	19,952	17.0	0	10
Chester . . . .	42,318	17.3	12.4	86
Coatesville . . . .	15,541	13.2	13.7	11
Connellsville . . . .	16,299	12.4	0	11
Dubois . . . .	15,323	16.8	0	8
Easton . . . .	31,172	10.9	0	31
Erie . . . .	77,993	22.5	0	130
Harrisburg . . . .	74,737	9.8	7.7	71
Hazleton . . . .	29,473	23.6	0	20
Johnstown . . . .	72,405	27.6	0	64
Lancaster . . . .	52,021	6.8	0	60
Lebanon . . . .	22,159	6.5	0	24
McKeesport . . . .	49,087	29.6	0	35
Meadville . . . .	14,132	12.3	0	13
New Castle . . . .	42,697	23.8	0	30
Oil City . . . .	19,969	13.4	0	15
Pottsville . . . .	23,060	10.5	0	38
Pittsburgh . . . .	593,300	26.3	4.8	738
Pittston . . . .	19,351	29.2	0	14
Philadelphia . . . .	1,761,026	24.7	5.5	3389
Reading . . . .	119,249	9.2	0	118
Scranton . . . .	152,283	27.0	0	124
South Bethlehem . . . .	25,512	41.9	0	39
Shenandoah . . . .	30,305	40.6	0	18
Shamokin . . . .	21,217	14.2	0	20
Sunbury . . . .	17,062	2.0	0	15
Williamsport . . . .	34,437	7.3	0	31
Wilkes-Barre . . . .	77,892	24.0	0	77
York . . . .	53,884	3.6	0	56
Steelton . . . .	15,968	32.7	9.0	19

DEATH-RATE FROM PULMONARY TUBERCULOSIS PER 100,000  
POPULATION DURING 1917. CITIES IN UNITED STATES.

The registration area . . . . .	128.9
Registration States . . . . .	126.8
Cities in registration States . . . . .	138.2
Rural part of registration States . . . . .	116.6
The registration cities in non-registration States . . . . .	156.6
All registration cities . . . . .	140.7

## REGISTRATION CITIES OF 100,000 POPULATION OR MORE IN 1910.

Place.	Rate.
Birmingham, Ala.:	
W. . . . .	51.0
C. . . . .	381.0
Baltimore, Md.:	
W. . . . .	148.9
C. . . . .	567.4
Boston, Mass.	149.1
Bridgeport, Conn.	153.9
Chicago, Ill.	133.2
Cincinnati, Ohio	211.7
Cleveland, Ohio	151.5
Denver, Col.	222.8
Detroit, Mich.	137.5
Los Angeles, Cal.	179.7
Louisville, Ky.:	
W. . . . .	104.2
C. . . . .	345.9
Minneapolis	119.2
Memphis, Tenn.:	
W. . . . .	115.0
C. . . . .	472.0
New Orleans, La.:	
W. . . . .	193.0
C. . . . .	560.0
Newark, N. J.	146.4
New York . . . . .	159.6
Bronx Borough . . . . .	201.1
Brooklyn Borough . . . . .	145.1
Manhattan Borough . . . . .	160.9
Queens Borough . . . . .	154.0
Richmond Borough . . . . .	184.4
Portland, Oregon . . . . .	49.9
Philadelphia, Pa. . . . .	175.0
Pittsburgh, Pa. . . . .	128.5
San Francisco, Cal. . . . .	162.4
Scranton, Pa. . . . .	69.5
Seattle, Wash. . . . .	57.0
St. Paul, Minn. . . . .	114.5
Washington, D. C.:	
W. . . . .	104.2
C. . . . .	345.9

**Conclusions.** What methods shall be used to improve the home conditions and occupational environment of our people?

1. If the children are to be the sanitarians of the future, there must be systematic health instruction in the public schools. Carrying out this idea the Pennsylvania State Department of Health purposes to furnish data on this subject to the Pennsylvania State Department of Public Instruction for a book which will be used throughout the extensive school system in this State, so that every school child will not only be taught this major branch but will be compelled to pass an examination upon its completion. Also the State Health Department is developing a public health school which is to be conducted by means of the daily and weekly newspapers and is comprised of twenty-four lessons on topics such as tuberculosis, school hygiene, milk, sanitation, the dinner bucket,

colds, flies and others, written in a style to appeal to the public generally. The State will be organized with classes, each community having its secretary, who will manage the affair. It is to be hoped that the children as well as adults thus instructed will not be satisfied to continue to live in an atmosphere or environment, which they can improve by putting into execution some of the knowledge obtained. It is not only important to teach people certain truths, but to see that they make practical use of them. Many of the well-recognized principles of preventive medicines are thoroughly understood by the laity, but their practice is sadly neglected.

2. More publicity is needed, so as to place the needs of a town or city before the general public, who may be ignorant of existing conditions. By the demand of the public many evils, such as overcrowding, improper sanitation and poor ventilation in public places, are eradicated and additions for the public good, such as fresh air schools, are obtained.

3. Greater effort should be made in connection with the establishment of fresh-air schools, and rounding up in the communities and rural districts the children, who are pre-tuberculous or in the active process of the disease and in providing treatment for them. It is hoped that in the future all schools will be conducted on the fresh air plan.

4. It is important and necessary that employers be kept reminded as to their duty to their employees. Rest rooms should be provided where a little recreation and relaxation may be obtained during the lunch hour. In many places firms are providing hot lunches at a reasonable rate to their employees, which does away with the carrying of cold articles of food and likewise provides relaxation at meals under favorable conditions.

5. The establishing of health centers in each of our cities and in representative towns of the rural districts, which shall be the centers of all activities pertaining to the uplift of the community. These centers in Pennsylvania are utilizing the rooms used by the State Clinics and the organizations that are engaged in this work are composed of individuals who are endeavoring to do their share in their particular spheres. Stated meetings are held which are attended by chiefs of the tuberculosis, genito-urinary, child welfare and prenatal clinics, the county medical director and representatives from the health council comprised of the American Red Cross, Associated Charities, Women's Clubs and Societies, Men's Clubs, including the Rotary and Kiwanis Clubs, Chamber of Commerce, Fraternal Organizations, Churches and Newspapers. At these meetings all social problems are considered and plans made to better existing conditions. Nutrition classes are being started and children from twelve to sixteen years of age are taught to cook; also mothers' clubs where lessons in sewing, planning meals and care of the baby

are given; also little mother's leagues where girls are taught how to clothe, feed and bathe the baby.

6. It is important to constantly keep before the public, sick or well, the value of sunlight. Sunlight is needed by all, in fact all measures upon which we rely for the cure of tuberculosis are those which we should recommend to the well in order to make them stronger, happier and more vigorous. In the recent research work of Sweany and MacLane,<sup>6</sup> Chicago, it was shown they found that a suspension of tubercle bacilli in salt solution was killed in twenty minutes in direct sunlight with the rays of the sun at an angle of 50 degrees; five hours in a film of dust in direct sunlight: five days in a film of dust in a south room and seven days in a film of dust in a north room. Soparker<sup>7</sup> has also performed noteworthy experiments, his work consisted in testing the resistance of tubercle bacilli under varying conditions such as sunlight, diffuse daylight and darkness. He found that the tubercle bacilli will live twenty days in moist sputum; three hundred and nine days in the dark; five days in diffuse daylight in dust and two hours in direct sunlight in dust. His work shows clearly that sunlight is the worst enemy of tuberculosis.

7. We recoil in horror from the leper house or the cholera camp, yet the deadliest known hotbed of horrors, the spawning ground of more deaths than cholera, smallpox, yellow fever and bubonic plague combined, is the dirty floor of the dark, unventilated living room, whether in city tenement or village cottage, where children crawl and elders spit. However we may improve the most insanitary house or room, make it habitable for either sick or well, but if we neglect to improve the occupants of the house, all our efforts will be of no avail. Every sanitary housing plan which does not take into account the sanitation or personal hygiene of its occupants must fail. They are inseparable. Sanitation of the house must go hand in hand with personal family hygiene.

8. Instead of Nature being able to cure tuberculosis unaided, as a matter of fact she has neither the ability nor the inclination to do anything of the sort. There is no class of patients whose recovery depends more absolutely upon a most careful and intelligent study and regulation of their diet, of every detail of their life throughout the twenty-four hours and of the most careful adjustment of air, food, heat, cold, clothing, exercise, recreation, by the combined forces of sanitation, nurse, and physician. It is only by education and education of the highest type that we have any reasonable prospect of cure.

9. Finally, it is the duty of every physician to influence public opinion, that the evils incident to bad housing, occupational environment and sanitation may be improved, so that the children, the hope of the future, may be given a chance.

<sup>6</sup> Loc. cit.

<sup>7</sup> Soparker, M. B.: Indian Jour. Med. Research, Calcutta, 1917, iv, 627-650.

## REVIEWS

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**SYMPTOMS IN THE DIAGNOSIS OF DISEASE.** By HOBART AMORY HARE, M.D., B.Sc., Professor of Therapeutics and Diagnosis in the Jefferson Medical College of Philadelphia; Physician to the Jefferson Medical College Hospital; one time Clinical Professor of Diseases of Children in the University of Pennsylvania; Commander, U.S.N.R.F.; Author of a Text-book of Practical Therapeutics and a Text-book of the Practice of Medicine. Eighth edition, thoroughly revised. Pp. 562; 195 illustrations and 9 plates. Philadelphia and New York: Lea & Febiger, 1920.

THE eighth edition of this standard work of Dr. Hare has been gone over thoroughly and carefully revised. Like the other works of which he is the author, and which have attained to many editions, this present volume shows that when revision is spoken of it is in truth a real revision. One of the secrets of the large number of editions that his works total is that in all things the author is a thorough student and omniverous reader. He keeps thoroughly up to date in the current medical literature, and from his knowledge of the literature that has gone before and of the valuable achievements in medicine in the past he is enabled to sift out the wheat from the chaff and give to his readers only those facts and elements which in his mature judgment are valuable.

This eighth edition follows very much the same general line as did the previous ones. The author takes up in detail in the early chapters the symptoms that arise in the various parts of the body, and in the latter chapters describes even more minutely what may be called the leading symptoms. There are two things which, added to the book, would seem to the reviewer to enhance its value. The first of these would be a brief discussion of the genesis of the various symptoms; the second suggestion is that the chapter on pain be discussed more fully and more completely.

The book is to be recommended most highly. The subject-matter as it is arranged and discussed is certainly presented in such a way that it will be most valuable to those most interested in the diagnosis of disease. The illustrations and typographical work leave nothing to be desired.

J. H. M., JR.

TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS.  
Vol. XXXIV. Philadelphia: Printed for the Association.

THIS volume contains either in entirety or in abstract the papers presented at the Thirty-fourth Session of the Association of American Physicians. A year has elapsed since the meeting was held at Atlantic City. Most of the papers, and indeed probably all of them, have been published in some medical magazine.

Almost every phase of internal medicine is covered by these articles. Many of them deal with observations and conditions consequent upon military service. Trench fever, war nephritis, effort syndrome and pneumonia are dealt with by ex-members of the medical corps. Lethargic encephalitis and influenza, too, are taken up in several papers.

A noteworthy contribution is the one on "The Influence of Dr. Osler on American Medicine." Dr. George M. Kober deserves much commendation for his excellent record of the life and service of our great English doctor.

The members of this Association are to be congratulated upon the uniform excellence of the presentations. This is so all the more because they represent the work done during a war year when there is a big tendency to be discouraged in individual endeavor. Dr. McCrae as Secretary of the Association deserves much credit for the able manner in which this volume has been edited. T. G. S.

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THE TRANSMUTATION OF BACTERIA. By S. GURNEY-DIXON, M.A., M.D. (Cantab.), M.R.C.S. (Eng.), L.R.C.P. (Lond.). Pp. 179. Cambridge University Press, 1919.

THE author presents the material in this book as his thesis for the degree of M.D. at the University of Cambridge. It is a collection of references from English and a very few other sources, to which Dr. Gurney-Dixon has added a series of his own experiments.

It is unfortunate that at the time of collecting his notes the author did not have at his disposal the original articles of Kruse and of Cohn, to whom we owe the present idea of bacterial specificity, but who recognize the variations possible in a single-celled organism the generations of which can be changed many times in the span of a day. The author's conclusions, however, would indicate that he realizes the inability of anyone to distinguish between variation and mutation until we are able to define a species. It seems to the reader that more emphasis might be laid upon evolutionary mutation and the possibility that some of the variations might be explained by considering that the bacteria were spores or degen-



erated strains. Many instances of variation are given, most of which can be explained upon technical grounds. Surely no evidence is adduced of a true mutation according to De Vries. The author offers the suggestion that there is a considerable chance of bacteria changing their enzymes without their essential natural history undergoing mutation. Since ferments are fluid it does not seem well for them to be considered one of the principal criteria upon which species are based. The book is nicely printed and the references to literature in English are numerous. H. F.

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MANUAL OF TROPICAL MEDICINE. By ALDO CASTELLANI, London School of Tropical Medicine, and ALBERT J. CHALMERS, Director, Wellcome Tropical Research Laboratories (Soudan Government). Third edition. Pp. 2436; 925 illustrations. New York: William Wood & Co., 1920.

THE new and greatly enlarged edition of this truly encyclopedic work has been thoroughly revised and offers 700 additional pages of matter and 300 more illustrations. The same general arrangement has been retained as in earlier editions. The first part deals with such introductory subjects as climate, races of man and foods, and treats of these in a way which is both scientific and interesting. The second part discusses the causes of diseases of the tropics, taking up the various poisons, protozoa, metazoa and vegetable parasites of etiological importance. The material here has been greatly added to and constitutes in its amplitude a work by itself. The third part considers the various diseases as such, dividing them into fevers, general diseases and diseases of the several systems. Here also many additions have been made, among which are morbid conditions associated especially with warfare.

The most enthusiastic approval is due the authors for the masterly completeness of this work. Its supreme position as a reference book of tropical diseases cannot be questioned. The subjects are discussed from every angle, the etiological aspects being particularly developed as the result of personal observation by the author.

The most obvious criticism is, of course, the prodigious thickness of the volume. Frankly, 2436 pages are decidedly too many to be included between two covers. The authors themselves recognize this fact, but believe that a two-volume work does not suit the conveniency of practitioners in tropical countries. This is perhaps true, but surely the present acknowledgedly unwieldy volume will suit them even less. The large size is due chiefly to the amount of repetition inevitable in treating the causes of disease apart from diseases themselves. It is surely evident enough

that if the two are to be considered as distinct subjects one volume should be devoted to general and one to special pathology.

Perhaps a more serious objection to the present edition is to be found in the ruthless revision which the protozoa have suffered. The authors, in former editions, have already developed a deplorable tendency to split up well-known genera into several new ones, and for familiar names, such as ameba, to substitute newer ones, such as loeschia. The objection here lies not merely in the great inconvenience to scientific workers in relearning a nomenclature at the appearance of each new edition of a standard work, but also in the very unfortunate substitution for a Greek or Latin name of significant derivation, of the name of an individual which has no etymological significance whatever. Now the new edition of this work not only discards the name trypanosoma for the human forms—while retaining it for the animal forms—but substitutes for it the name of the author! So Trypanosoma gambiense becomes Castellanella gambiensis and the rhodesian form C. rhodesiensis. Surely a most indelicate proceeding. One form is actually named Castellanella castellanii. M. McC.

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DISEASES OF THE CHEST AND THE PRINCIPLES OF PHYSICAL DIAGNOSIS. By GEORGE W. NORRIS, A.B., M.D., Assistant Professor of Medicine in the University of Pennsylvania, and HENRY R. M. LANDIS, Assistant Professor of Medicine in the University of Pennsylvania, with a chapter on Electrocardiograph in Heart Disease, by EDWARD KRUMBHAAR, Assistant Professor of Research Medicine in the University of Pennsylvania. Second edition. Pp. 844; 433 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

WITH the advent of the second edition of this work the medical profession has at its disposal the best book upon physical diagnosis in diseases of the chest so far published. In this edition much material has been added. All our knowledge gained during the world war, insofar as diseases of the chest are concerned, has been included. The newer conceptions of the influenzal and streptococcic pneumonias and empyemata, as well as spirochetal bronchitis, chronic inflammatory conditions of the lungs of uncertain etiology, calcification of the lungs have been added.

The many noteworthy features of the first edition have all been maintained. A large space has been given to diagnostic acoustics. In so doing the authors have put the art of diagnosis upon a good physical basis, and in a way so that the student can interpret his findings in a pathological manner. The book is magnificently illustrated. The photographs of the frozen sections show the

relationship of various anatomical parts as related to physical diagnosis in a most admirable way. The diagrammatic illustrations are all very clear. Various instrumental diagnostic methods are included, but only those which have proved their clinical worth. The chapter on the electrocardiograph is especially to be mentioned under this heading. It is very clear and concise, and is that portion of our newer method of cardiac study with which all students should be acquainted. Another chapter is given up to the diseases of the diaphragm, a portion of our examination which is only too often passed over entirely.

The book is a great deal more than the usual book upon physical diagnosis. In all cases a definition of the disease under consideration, as well as its etiology, morbid anatomy, symptoms and a final diagnosis, is given. The book shows throughout a most careful and painstaking compilation. The authors are to be congratulated, as this book is one of the greatest steps forward in securing for our patients better and more scientific medicine.

T. K.

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SEXUAL IMPOTENCE. By VICTOR G. VECKI, M.D. Sixth edition. Pp. 409. Philadelphia and London: W. B. Saunders Company, 1920.

THIS, the sixth edition of Vecki's book, partakes of the recognized standing of the previous editions as one of the accepted authoritative writings on the subject. The material is presented with practically no change in its arrangement and the author has incorporated but twelve new references from the literature of the past five years. The subject of endocrinology, however, is entered into with greater fulness and with a more positive knowledge of its therapeutic value. It is strange that the author continues to use words of questionable etymological correctness such as sperma, diphtheritis, catarrhalic, prostata, centra, sexualibus, et cetera, as they distract the attention and destroy the pleasure of reading. Likewise, one notices the omission in this edition, as in its predecessors, of a more thorough exposition of chronic prostatitis in its relation to impotence, and the same might be said of syphilis. Lallemand and his dread "spermatorrhea" still occupy the center of this author's stage, though in the practice of most urologists both have been long since relegated to the minor role of interesting historical personages in the light of modern pathological study. The book has gained four pages over its predecessor, though retaining its usual size, binding and excellence of workmanship in publication.

A. R.

MANUAL OF NURSING PROCEDURE. By AMY E. POPE, Visiting Instructor, San Francisco, Calif. Pp. 596; 52 illustrations. New York: G. P. Putnam's Sons.

THIS *Manual of Nursing Procedure* is the latest of a series of works by the same author, all of them prepared especially for the use of nurses both in training and as reference books after graduation. All of the procedures which a nurse practices are taken up in eighteen chapters, with an added glossary and index. Each chapter has in mind a supplemental demonstration by the teacher covering the subject-heading. It includes a description of this demonstration and questions which can be put to the pupil nurses, together with directions for treatment, precautions and other important information. The text is characterized by brevity, combined with clearness of diction, and should be a splendid book for a nurse in training. The writer had the privilege of reviewing the *Anatomy and Physiology for Nurses* by this same author, and he feels that the present work is not only up to the previous standard, but indeed considerably improved.

GENERAL AND DENTAL PATHOLOGY. A TREATISE FOR STUDENTS AND PRACTITIONERS. By JULIO ENDELMAN, M.S., D.D.S., Professor of Special Dental Pathology, College of Dentistry, University of Southern California, etc., and A. F. WAGNER, A.M., M.D., Professor of General Pathology, College of Dentistry, University of Southern California, etc. Pp. 593; 440 illustrations and 4 colored plates. St. Louis: C. V. Mosby Company, 1920.

THE intention of the authors, according to the preface, is to impart a foundational knowledge of the subject by rendering less complicated the interpretation of pathological phenomena in the field of dental diagnosis. The book is divided into two distinct—I almost said *too* distinct—parts, general pathology by Wagner and dental pathology by Endelman.

Part I is an able presentation in easily assimilated form of the principal facts of pathology, freely illustrated by cuts taken for the most part from standard works on this subject. There are one or two conspicuous omissions, notably the leukemias, about which not a word appears, although considerable space is given to other topics of less direct importance to the dental student, *e. g.*, tape-worms. In the chapter on tumors practically no reference is made to those new growths which are particularly prone to affect the mouth and jaws. Odontomata are dismissed with the brief but erroneous definition of "tumors growing from the pulp of teeth." Further elucidation of the pathology of these particular growths

are looked for in Part II, but in vain, with the exception of an admirable chapter on cystic odontomas by New. The important group of calcified and other solid odontomas receives no mention whatever.

Part II, by Endelman, is a detailed discussion of the pathology of the teeth and adjacent structures, with many excellent original illustrations. Although a digression from the strict limits of the subject, the value of the work is increased by the stress laid upon the clinical aspect of the various diseases. Here, again, there appear to be some important omissions, of which the odontomata have already been referred to. Ulceromembranous gingivitis, due to Vincent's organisms, is not considered as a pathological entity.

One gains the impression that we are dealing here not with one book but with two distinct books under the same cover, each well written in itself, but with little or no evidence of coördination of the two parts. On such a fundamental condition as abscess, for example, the authors appear to present a direct conflict of ideas. Wagner, on page 102, properly defines an abscess as a cavity filled with pus surrounded by a wall of inflammatory tissue. Endelman, on the other hand, classifies all continued infections of low virulence located in the peridental membrane as chronic dento-alveolar abscesses, whether they are suppurative or not, on the ground that pathologically they are all reactions to the same character of infection. By this reasoning the various stages of reaction to any infection that could eventuate in abscess formation should be termed abscess.

With a little more stress upon the dental and oral application of general pathological facts, the supplying of the omissions noted, and the correction of seeming divergence of ideas on the part of the two authors the book should serve a useful purpose as a textbook for students.

R. H. I.

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THE TREATMENT OF SYPHILIS. By H. S. BAKETEL, A.M., M.D., Long Island College Hospital, and Medical Director, H. A. Metz, Laboratories. First edition. Pp. 158; 14 illustrations. New York: The Macmillan Co., 1920.

With the close of the present decade comes our first opportunity to draw definite conclusions as to the efficiency of our modern therapy of syphilis. The dream of a *therapia sterilisans magna* (Ehrlich) has gone and medicine is faced by a duty to rid coming generations of this plague by the energetic employment, in an approved manner, of the truly powerful medicaments at our disposal. Dr. Baketel's book presents this information. His creed is: Eternal vigilance is the price of freedom from the *Spirocheta pallida*. Immediate, consistent, persistent and proper treatment

is necessary to overcome the ravages of syphilis. The third and fourth chapters present an interesting exposition of the history and chemistry of salvarsan and neosalvarsan. Chapter VI outlines a good working plan of treatment, while subsequent chapters deal with the technic of the intravenous administration of the arsenical preparations; the reactions and accidents; the interpretation of the Wassermann test as a guide to treatment; the special handling of congenital, visceral and neurological syphilis. The author is strongly wedded to the arsenical preparations, for he disposes of the time-honored internal administration of mercury by the words, "We mention this method only to condemn it, and believe the physicians who pursue this line of treatment are following an *ignis fatuus*," and likewise the intravenous mercury administration by saying, "This is not yet sufficiently perfected to permit of discussion of a helpful nature;" while seven pages are devoted to an attempt to inspire confidence in the innocuousness of the varying methods of intramuscular salvarsan. Nor can we agree with the advice to stop treatment on the first negative Wassermann (pages 38 and 86). The book is fully illustrated and carefully published.

A. R.

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DISEASES OF INFANTS AND CHILDREN. By HENRY DWIGHT CHAPIN, A.M., M.D., and GODFREY ROGER PISEK, M.D., Sc.D. Fourth revised edition. Pp. 592; 195 illustrations. New York: William Wood & Co.

IN this new edition the authors have succeeded not only in keeping up the excellence of former editions, but in adding new material which brings the volume well up to date. There is a large store of valuable information contained between its pages.

As usual in works on pediatrics the initial chapters deal with the newborn and the diseases of this period of life as well as with the injuries during birth. The next two sections of the book consider, respectively, the hygiene of infancy and the examination of the sick child. Here the special examinations of the sputum, gastric contents, feces, cerebrospinal fluid, urine and blood that are of value in pediatrics are given. The lesions in children in which the roentgen ray may be used as an aid in diagnosis are outlined. An excellent chapter on general therapeutics is included. Following is the important section on infant-feeding, and here one finds much of value in the chapter dealing with practical feeding. The problem is handled in a safe and sane manner, entirely free from the viewpoint of the faddist or extremist. Next is the section taking up the infectious diseases, including syphilis, tuberculosis and the common contagious diseases. In order after this come the sections on diseases of the respiratory tract, diseases of the circulatory system and diseases

of the blood and the ductless glands. Under general diseases of nutrition are included rachitis, scorbutus, marasmus and diabetes, and the authors also describe the condition of congenital or prenatal rachitis. One should mention also the sections on diseases of the uropoietic system, diseases of the genital organs and bladder, diseases of the nervous system, congenital malformations and deformities, the commoner surgical diseases, diseases of the ear and eye and diseases of the skin.

A. G. M.

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THE MEDICAL CLINICS OF NORTH AMERICA. Vol. III, No. 5.  
Pp. 1167 to 1492. Philadelphia and London: W. B. Saunders Company, 1920.

THE present number of *Medical Clinics of North America* is composed of contributions from the Jefferson and University of Pennsylvania Medical Schools. The number opens with a short discussion by Dr. Deaver on chronic appendicitis. The next six articles are from the Jefferson Hospital staff, and they are all extremely interesting and valuable contributions to clinical medicine. Dr. McCrae discusses most thoroughly the question of low blood-pressure, and emphasizes the fact that it is an extremely important symptom which should not be disregarded because we are accustomed to think that a cause must be found and treatment is necessary, only if the pressure is high. Dr. Beardsley contributes a well-written article on chronic valvular heart disease and a very stimulating and scholarly essay on "Ethics, Ideals and Efficiency in the Practice of Medicine." The remaining articles are written by the members of the staff of the University Medical School. Dr. Stengel writes on the treatment of valvular heart disease before failure of compensation. Dr. Riesman discusses edema of the lungs; Dr. Landis, meningitis; Dr. George Norris considers syphilitic aortitis from its various standpoints. Dr. Musser describes three cases: one of aneurysm, one of pericarditis, lastly one of aplastic anemia. Dr. Sailer contributes an article on mumps, which is particularly valuable on account of the opportunity that he has had of studying a very large number of these cases during an epidemic in one of the cantonments. Dr. Goodman writes on heart murmurs and Dr. Pepper on jaundice as an early symptom of heart disease, while Dr. Hopkins discusses the treatment of jaundice. Dr. Farr describes painless gastric crises and Dr. Doane details the work he has performed in the Philadelphia Hospital in the treatment of drug inebriety.

J. H. M., JR.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**The Nature, Prevention and Treatment of Heat Hyperpyrexia: the Clinical Aspect.**—WILCOX (*British Med. Jour.*, 1920, p. 392) has recorded his observations of the influence of heat on troops in Mesopotamia during the summers of 1916, 1917 and 1918. In the region of the Persian gulf, heat-stroke is more frequent than in India, although the temperature is about the same. With temperature of 110° F. in the shade heat-stroke makes its appearance, and with every degree above this the number of cases increases. If the humidity is low the incidence of heat-stroke is less than in damp regions at the same temperature. Thus in Bagdad, where the humidity is low, the case mortality was 8.4 per cent. in 1917 and 5.4 per cent. in 1918, while in India the mortality (case) was 10 per cent. in 1918 and 8.1 per cent. in 1917. Heat-stroke occurs much more frequently and is more severe in men past forty years of age. The incidence was also greater among the British than among natives. During the hot days the water intake reached 9 to 13 liters per day per man, and unless this amount was obtainable heat symptoms appeared. The cause of heat symptoms is referred to intoxication due to the influence of heat on the organism. Acidosis plays no role. The pathologic findings were: Edema of brain and cloudy swelling of liver, kidneys and myocardium. There are four types of disease produced by heat. (1) Heat exhaustion with weakness, fainting, tachycardia, slight fever or at times subnormal temperature; the mortality is small. (2) Gastric Type: with suffused face, irritability, nausea and vomiting. Temperature and pulse are often normal. The



knee-reflexes were absent in the 9 cases (16 per cent. of total of severe cases) of this type. (3) Choleraic Type: Sudden collapse, slight fever, vomiting, diarrhea, cramps in abdomen and extremities. The mortality is high. This group comprised 11 per cent. of the severe cases. (4) Heat Hyperpyrexia: This was the most common type (72 per cent. of the severe cases). The onset is often sudden. The temperature may reach 110° F., with loss of consciousness. In other instances the onset is gradual, with headache, cyanosis, muscular cramps and Cheyne-Stokes respirations. Lumbar fluid is clear. The fever, if recovery ensues, returns to normal after a few days.

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**A Report of Eleven Cases of Cervical Sympathetic Nerve Injury Causing the Oculopupillary Syndrome.**—COBB and SCARLETT (*Arch. Neur. and Psych.*, 1920, iii, 636). The authors have had opportunity to study the Claude Bernard-Horner syndrome in eleven cases of war wounds, especially in its relation to peripheral nerve and medullary injury. Details of the cases and anatomical facts of importance will be found in the article. Enophthalmos, ptosis and miosis are practically a constant finding on the affected side. The ocular tension was below normal in five cases. Sudomotor disturbances were present in about 50 per cent. of the cases and vasomotor disturbances in only two cases. The conclusions drawn from the study indicate that root lesions (C VII, VIII and D I) cause the most severe and typical Horner syndromes. Partial or complete lesions of the cervical sympathetic produce less severe symptoms referable to the eye. Contusion of the cord produces a mild Horner complex which is more prone to recovery.

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**Contribution to the Study of Uremic Hemorrhagic Rectocolitis.**—BENSAUDE, CAIN and ANTOINE (*Ann. de méd.*, 1920, vii, 41) report two instances of hemorrhagic colitis in the course of uremia. In both instances autopsy performed shortly after death disclosed the presence of extensive indolent ulcers in the colon and rectum, which were undoubtedly the cause of the extensive rectal hemorrhages observed during life. The relation of the intestinal changes to the renal insufficiency is not clear. In conclusion, the authors emphasize the variation of symptomatology in the cases and call attention to the fact that uremic ulceration of the bowel may give no clinical symptoms. In suspicious cases, however, proctoscopy may lead to a correct diagnosis.

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**Fetid Spirillar Bronchitis and Pulmonary Gangrene.**—NOLF (*Arch. Int. Med.*, 1920, xxv, 429) reports eleven cases of what he calls hemorrhagic bronchitis with spirochetes. Of these nine were primary. The disease attacks men in good health. Usually the first symptom is a chill. There are malaise, bone pains and cough with pain in the chest. There are signs of a general bronchitis. The fever rises, cyanosis appears and the patient loses strength. The sputum becomes purulent and fetid and rarely hemorrhagic. In the sputum there are few or many spirilla. Their relative number parallels the severity of the disease. The spirilla stain well only by special methods. They resemble closely Vincent's spirillum. In many instances other organisms are present. The disease shows no tendency to spontaneous cure. The whole ques-

tion of the role of the spirillum in the production of the disease is discussed at length and the author assumes that it is pathogenic and causal. However, he believes that the organism may lead a saprophytic existence in the mouths of healthy carriers. The institution of novarsenobenzol treatment leads rapidly to the destruction of organisms and amelioration of symptoms. For a comprehensive critical review of the literature of this subject the reader is referred to an excellent article by SOLOMON (*Ann. de méd.*, 1920, vii, 53), which is not suitable to abstract.

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**An Investigation of the Size of the Heart in Soldiers by the Tele-roentgen Method.**—COHN (*Arch. Int. Med.*, 1920, xxv, 499). In this contribution "teleo" heart measurements were made on 161 soldiers who have seen active service. The technical details were carefully chosen and may be found in the article. The conclusions drawn from the observations are as follows: (1) In normal breathing the difference in the size of the heart during inspiration and expiration may be neglected. (2) The use of the transverse diameter of the heart shadow is a satisfactory measurement. It is as useful as and less uncertain than the long diameter or the area. (3) The range of the observed measurements interferes with the usefulness for the clinic of standard and average curves. (4) The hearts of soldiers examined under the conditions stated (after active service in infantry) are not larger than those of normal individuals.

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## SURGERY

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UNDER THE CHARGE OF

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UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
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TO THE UNIVERSITY HOSPITAL.

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**Advantages and Disadvantages of Gauze Packing in Abdominal Operations.**—MAYLARD (*British Med. Jour.*, November 29, 1919, p. 556) says that the present attitude with regard to the use or non-use of gauze packing in abdominal operations is not unanimous. Careful and reasonable discrimination is needed to decide when a particular method of treatment should be employed and when it should be avoided. In considering the facts connected with the two sides of the subject, it may, in the first place, be stated, probably without contradiction, that the question of the use or non-use of gauze packing only arises in operations upon the abdomen where sepsis in some form is found to be present. These operations are concerned chiefly with the appendix and the female pelvic organs. The advantages of gauze packing are (1) the antiseptic effect obtained from the substance with which the gauze is impregnated, and (2) the stimulation of a healthy granulating

wound. One may not unreasonably infer that the beneficial effects obtained in the use of gauze packing for external wounds would accrue equally in the case of similar lesions occurring within the abdomen. But whatever the analogy between septic processes taking place within and without the abdomen, there is absolutely none between the parts involved, since the peritoneal cavity with its viscera introduces an entirely new aspect. The author reports his experience with a piece of dry gauze used to pack away the small bowel during a pelvic operation. Within one-half an hour it had become intimately adherent to the visceral peritoneum and left an acutely inflamed surface when peeled off. Two cases are reported in which gauze inadvertently left in the peritoneal cavity later ulcerated into the intestine. The author has frequently noted that on the withdrawal of a gauze pack which had been left in the wound for a few days after the operation a fecal discharge has, if not immediately, in a day or two ensued. The author thinks that if the gauze packing be previously wrung out of a warm saline or citrate solution this rapid adhesive effect would not have been produced. Four other disadvantages, more or less related to the length of time the gauze is retained, are noted: (1) If the packing is employed in septic cases without the adjunct drainage of a tube the gauze may act as a dam; (2) the irritating effect of gauze on neighboring coils of healthy bowel leads to a low form of adhesive peritonitis which may end in obstruction; (3) the longer the wound is kept open the more likely is the chance of a ventral hernia; (4) the withdrawal of gauze is a very painful process. The author thinks that the disadvantages greatly outweigh the advantages and that gauze packing should be avoided except under definite and clear limitations, which may be expressed thus: the use of as small a piece of gauze as possible, which equally connotes the avoidance of large packs retained for several days.

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**Recurrent Nephrolithiasis.**—LAMSON (*Ann. Surg.*, 1920, lxxxi, 16) says that we cannot hope to prevent recurrence of this disease unless we know more of its true etiology. Careful study of the history of the patient in all its different aspects and thorough examination of the urine and chemical analysis of the stone may determine the postoperative treatment. Thorough flushing of the urinary channels by drinking freely of water, preferably distilled water, may help in the dislodgment and removal of any possible nucleus of future stones. This treatment must be continued for a considerable period even after the urine has completely cleared up. Faulty or incomplete surgery by leaving in the pelvis fragments of stones may contribute toward a recurrence of nephrolithiasis.

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**Life Expectancy of Patients following Operations for Gastric and Duodenal Ulcer.**—BALFOUR (*Ann. Surg.*, 1919, lxx, 522) says that in the past surgical treatment of many diseases has been measured by operative mortality and the permanency of the relief: However, life expectancy can be said to be the major consideration with the patient. The percentage of operative deaths in the hospital following operations for gastric ulcer was twice that following duodenal ulcer, but both percentages are low. The mortality during the three years following the operation among persons operated on for gastric ulcer was three times

as high as that among persons operated on for duodenal ulcer. The mortality among persons operated on for gastric ulcer decreases relatively after operation, but the data are not sufficient to determine the number of years which must elapse before the death-rate is similar to that of the general population. The mortality among those operated for duodenal ulcer in this series was less than that among the general population.

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**Life History of the First Case of Myxedema Treated by Thyroid Extract.**—MURRAY (*British Med. Jour.*, March 13, 1920, p. 359) says that his patient, first given the thyroid extract in 1891, at the age of forty-six years, died recently at the age of seventy-four years. The results in this afforded definite proof that the thyroid gland produced an internal secretion and showed that the thyroid insufficiency of myxedema in man could be made good by maintaining an adequate supply of thyroïdal hormones from an external source. The patient was given a hypodermic injection of twenty-five minims of the extract twice a week at first, and later on longer intervals. Three months later she was much improved and after this the injections were given fortnightly. Still later she was given 10 minims by mouth six nights a week, so that one dram was consumed in the course of a week. On this dose she remained in good health, and free from the signs of myxedema. Murray has seen the patient only once during the last eleven years, but another physician kept track of her and reported that she continued to take the thyroid extract regularly until early in 1918 when it became difficult to obtain, so that she was given dry thyroid extract in a tablet instead. She died early in 1919 from cardiac failure. This patient was thus enabled, by the regular and continued use of thyroid extract, to live twenty-eight years after she had reached an advanced stage of myxedema.

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**Arteriovenous Fistula with an Analysis of 447 Cases.**—CALLENDER (*Ann. Surg.*, 1920, lxxi, 428) presents a very valuable study of this subject and reviews the literature thoroughly. Under treatment he deals with the various methods which have been employed and gives statistics concerning the results in each instance. He says that the operation of complete extirpation of the aneurism after quadruple ligation of the afferent and efferent vessel, with its high percentage of favorable results, must be duly accredited. In 122 such operations there had been 117 cures, or 95.9 per cent., 1 death, or 0.8 per cent., and 1 residual gangrene, or 0.8 per cent. Death occurred in Barendrecht's case in the popliteal vessels, and failure resulted in Jaboulay's case of posterior tibial aneurism. Among the cases of improvement may be mentioned the popliteal aneurism operated on by von Eiselsberg, in which there were residual plaques of gangrene of the foot, and Bernhaupt's aneurism of the popliteal vessels with residual motor and sensory changes, and Eiselsberg's brachial aneurism, which showed symptoms after three years. In this type of operation the disadvantages of tardy healing and imperfect hemostasis, as well as gangrene from pressure on arterial collaterals, which in other operations are so major, are here reduced to a minimum. By careful dissection one may obviate the useless

section of adherent nerves and vessels, whose loss plays so important a role in the formation of residual nerve and trophic disturbances. In general, it fulfils all requirements, presents the least danger, and has given up to the present the best results. Most writers agree that the ideal operation is that which maintains the continuity of the vascular paths, and the procedures adopted are: ligation of the communication, lateral suture, and end-to-end suture.

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**The Wassermann Control in the Treatment of Syphilis.**—SARGENT (*Am. Jour. Syph.*, 1920, iv, 287) says that the Wassermann offers an excellent control in the treatment of syphilis only when taken in consideration with the physical findings and with the past history of the patient, including the amount of his treatment. Syphilis in the pre-Wassermann primary stage reacts most readily and surely to intensive treatment. Wassermann positive primary syphilis cannot be cured by a few injections of arsphenamine and a few months of mercury, but when treated intensively and over a long period, offers an excellent prognosis. There seem good grounds for the belief that many cases of secondary and tertiary syphilis even of years' duration, when treated intensively both with arsenic and mercury for one, two or three years can be rendered Wassermann negative and apparently cured. There are promises of some hope of rendering inherited syphilis permanently Wassermann negative by prolonged treatment with arsenic and mercury. In at least some cases of early tabes it is possible to render both the blood and spinal fluid negative to the various clinical tests.

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**The Significance of Chronic Vesiculitis in Prostatics.**—MARION (*Jour. d'Urologie*, 1920, ix, 11) reports three cases of prostatic disturbances in which the diagnosis was uncertain but in all of which the prostate was removed by the suprapubic route. They all showed evidence of tumor of the prostate but in every case the seminal vesicles were enlarged, abnormally painful and bosselated. On section they presented a series of cavities filled by a serum that was turbid and sometimes bloody. The walls were simply thickened. Marion thought this condition was due to a retrograde dilatation from occlusion of the ejaculatory duct by the prostatic tumor. He concludes that a vesicular induration, unilateral or bilateral, is a sign of tumor of the prostate. But one should not regard this induration of the vesicle as a prolongation of the prostatic tumor. In all the cases the operation was done as for hypertrophy of the prostate. The isolation of the vesicles was not difficult with the aid of the finger in the rectum. The operative results are much the same as after prostatectomy for hypertrophy. The establishment of painful swelling of the seminal vesicles in a prostatic ought to suggest the idea of cancer, but the painful swelling of the vesicles ought not to be interpreted, at least in a certain number of cases, as a sure extension of the prostatic neoplasm but simply as a retrograde dilatation of the vesicles, the ejaculatory ducts being invaded by the cancer. It does not contra-indicate removal of the tumor if this is possible. The removal of the seminal vesicles does not aggravate the prognosis of the prostatectomy.

## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

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**Hereditary Occurrence of Hypothyroidism with Dystrophies of the Nails and Hair.**—BARRETT (*Arch. Neurol. and Psychiat.*, December, 1919) reports a case in a family that for generations has shown among its members peculiar trophic disorders of the nails and hair, and various abnormalities of a mental or nervous character. The patient under observation showed a plumpness of the skin, which felt as if it were thickened in its deeper parts. Around the eyes the skin was puffy, as if from increased subcutaneous fat. The hands were chubby and the fingers were short and clubbed. The hands and the feet were cyanotic. The surface of the skin lacked moisture and the skin of the finger tips and the soles of the feet was exfoliated. There was a scant amount of hair on the head and body, and there was also a peculiar abnormality of the nails. The hair was thin and patches were covered only by a fine lanugo. The eyebrows were reduced to a few scattered hairs and these were stiff and short. The nails of the fingers and toes were lacking a quarter to a half an inch of reaching the tips of the fingers and toes. There was no lunula. The free margin was thickened and broken. The surfaces were smooth and not ridged. The nail bed was exposed and in places showed suppuration. Neurologically there was a tic-like movement of the face, and when he became emotionally excited there was a tic of the right shoulder. Speech was thick and nasal in quality. Bone conduction for sound was absent in the left ear. There was a high degree of hyperopia. On administration of thyroid extract marked improvement was noted. In the family history the same deficiencies were present for at least six generations. Of sixty-one members in the family the defect was present in fourteen. These showed the defect in both the hair and the nails. The nail defect was about the same in all of these, but there was much variation in the degree of the loss of the hair. There was usually an extreme scantiness, but in none was there a total loss. In the most extreme cases there was a fine lanugo-like covering for the scalp. The defect tended to occur in a mendelian type of distribution, but the varied character of the abnormalities appearing in relation with the type defect of nails and hair was too complicated to be explained in a simple mendelian formula. All the individuals having the defect gave a mixed progeny when crossed with normal mates. A high degree of feeble-mindedness and neurological disorders of a degenerative type were present. Of the members of the third generation who had dystrophies of the nails and hair their descendants numbered twenty-nine. Of these twenty-two were definitely abnormal. Twelve of these had the characteristic dystrophy and ten others who lacked this abnormality showed other constitutional and nervous disorders. These included 1 case of epilepsy, 1 case of hysteria, 1 case of severe tic, 4 cases of feeble-mindedness, 1 case of nocturnal

enuresis, and four died at an early age from marasmus. Those with nail and hair dystrophies showed other abnormalities. One had epilepsy, 1 had cancer, 4 were feeble-minded, and 1 had nocturnal enuresis. In the literature there are a few other observations on families showing similar dystrophies of the hair and nails. The earliest one of these and the most extensive in abnormalities was that reported by Nicolle and Hallipie. In this family of fifty-nine known persons, thirty-six showed the dystrophies. In 1896 White reported the study of a family in which there were fourteen members in four generations. Of these, seven showed the characteristic abnormalities. Eisenstaedt, in 1913, reported observations on a family of thirteen members, which showed the occurrence of the dystrophies in five generations. Among eight members of the fourth generation, the abnormalities were present in three. It is also probable that a contribution by Hoffman should be included in this connection. This reports a line of thirteen individuals, eight of whom through four generations had shown abnormally short and scant eyebrows and dystrophies of the nails of the hands and feet. In this family there were several instances of thyroid disease. The patient had a large struma and the same condition was present in her mother. The appearance of the mother suggested hyperthyroidism, and Hoffman commented that perhaps one might believe that a dysthyroidism was the predisposing cause for the described malformation. The frequency of disorders of the nails and hair in hypothyroidism is shown in several analyses of large groups of cases of myxedema. In an analysis of 150 cases, Hun and Prudden found malformation of the nails in 75 per cent. and in a later series Howard found the nails abnormal in 86 per cent., and the hair in 93 per cent. As to the heredity tendency of hypothyroid disorders there is much confirmatory evidence. In the series of Hun and Prudden 8 per cent. of the cases showed direct inheritance and in the series of Howard this was found in 6 per cent. of the cases.

**Reestablishment and Development of Breast Milk.**—MOORE (*Arch. Ped.*, December, 1919) reminds us that breast milk is the only baby food that stands both chemical and biological tests. It is a living secretion containing all the food requirements of the infant as well as the antibodies to infection. Statistics show that the death-rate of babies is several times as great among the artificially fed as among the breast-fed. Maternal nursing of all infants would therefore be a large step forward in the decreasing of infant mortality. The disadvantages of artificial feeding are noticeable not only in the death-rate among infants, but also in their physique and health as they grow older. Bow-legs, knock-knees, large epiphyses, rosary and Harrison's groove are readily demonstrable as evidence of improper feeding. The defects in the permanent teeth are also to be attributed to this same cause. He mentions the four methods of increasing the breast milk that has been used. They are drugs, diet, massage and expression. Practically every drug has been used for this purpose. The glandular products especially pituitrin are now being widely used. There have been careful physiological experiments made which show that pituitrin acts upon the smooth muscle fibers, causing them to contract and forcing the milk more rapidly from the breast. The amount of milk excreted in a given time is increased, but the twenty-four-hour total remains unchanged. There has long been

discussion as to the relation of diet upon the breast milk. The mother must have additional food to make up for the 750 calories lost with the milk and enough water to make up the quart of water secreted. It has been shown that if the mother has a glass of milk, one egg or its equivalent of meat, the protein content of her milk will be normal. The most common mistake is in overfeeding the nursing woman, especially with cow's milk. The effect of massage upon the breasts has long been known. It increases the flow of milk. The fourth method used is expression by hand. The author details the method as follows: First, place the balls of the thumb and of the forefinger on opposite sides of the nipple just outside of the areola, pressing them firmly against the gland itself. Second, maintaining this pressure, bring the thumb and forefinger together back of the base of the nipple, thus pressing the milk out of the sinus lactiferous or ampulla. Third, give a slight forward pull to empty these external ducts. Stripping or even touching the nipple is usually unnecessary. His further method is to give after each nursing the milk expressed at the previous nursing and in addition a complementary feeding from the bottle. This amount varies inversely as the amount procured from the breast. As the babies grow stronger they empty the breast more completely.

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**On the Complete Control of Epileptic Seizures by Luminal.**—DERCUM (*Therap. Gaz.*, September, 1919) first gave the drug in divided doses three times a day as in the common administration of the bromides. This made the patients a little heavy during the day and sometimes even dizzy. He found that if he limited the administration of the drug to one dose at bedtime, these symptoms did not appear and the efficiency of the drug was not impaired and possibly was increased. He found that the drug exerted a remarkable control over the seizures even in the most confirmed cases. The doses required were very small, a dose of  $1\frac{1}{2}$  grains of luminal or 2 grains of luminal sodium given at bedtime being sufficient. He was rarely obliged to give as large a dose as 3 grains. In a number of cases the use of luminal resulted in the abolition of the convulsive seizures for periods of from several months to several years. In the group of the "essential" or "morphologis" epilepsies, the efficacy of the drug proved most remarkable. The luminal acted virtually as a specific. At no time was there the slightest deleterious or untoward effect. There were no changes in respiration, circulation or temperature, and further there was no exciting of drug habit or craving, as the action of the remedy is free from either pleasurable or disagreeable sensations. In some cases luminal did not at once control the seizures, but sometimes it had to be given for a week or two before its full action was established. If small doses of bromides were given for a brief period at the beginning of the treatment, the action of the luminal began more quickly. In many cases the luminal was continued over many months and in a few instances over a period of one, two or more years. In some of the patients in whom either through a misunderstanding or through carelessness the luminal was discontinued for a time, the seizures did not recur. Luminal is a member of the group of drugs to which belong adalin, barbital and barbital sodium. Chemically it is phenylethylmalonylurea.



**Quantitative and Qualitative Changes in the Cerebrospinal Fluid of Various Diseases and Their Significance.**—LEVINSON (*Am. Jour. Dis. Children*, December, 1919) discusses in this paper a work which was undertaken with the view of determining whether there were any chemical and physicochemical changes in the cerebrospinal fluid of meningism in addition to the physical changes, which are very apparent, and whether the chemical and physicochemical changes noted in the cerebrospinal fluid of meningitis differ chemically and physicochemically only quantitatively and qualitatively as well as in the various forms of the disease. Particular attention was paid to acidosis. Kopetzky holds that the predominance of the pressure symptoms as found in meningitis is in large measure due to a state of edema of the cerebral and meningeal tissues, and the edema is the result of an acidosis evidenced clinically by the varying degree of acidity found in the cerebrospinal fluid. This study comprises 155 cases that presented some form of meningeal involvement. Of this number 100 specimens of fluid were obtained from cases of meningism, that is from cases in which there was a rigidity of the neck, a positive Kernig and Babinsky, but in which the meningeal symptoms soon subsided and an infection in some other part of the body made its appearance. Fifty-five fluids were obtained from various forms of meningitis, the greatest number coming from cases of meningococcic and tuberculous meningitis. In all of these fluids, the amount, the pressure, the number of cells, and the various tests for globulin increase were noted. In addition to these routine observations the fluids were also studied for the H-ion concentration, the alkaline reserve, the chloroid, the amount of lactic acid, and the presence or absence of acetone bodies. Of the 100 cases of meningism under observation, all showed an increase in the amount and pressure of the cerebrospinal fluid. The amount of fluid removed at one sitting varied between 15 and 40 c.c. compared to 10 c.c. which is the maximum which it is possible to remove in one sitting in normal cases that present no sign of meningeal irritation. The pressure varied from 200 to 700 mm. of water compared to 90 mm. in normal cases with the patient in the recumbent position. No sediment was found in any of the fluids. In 85 cases the cells numbered less than 6 per cent.; in 15 cases they were increased in number. The same was true of the globulin content, only 15 of the 100 cases showing an increase of globulin. The chlorids ranged between 0.6 and 0.74 gm. per 100 c.c. of fluid, which is the average range for normal fluid. Lactic acid was present in the amount as in normal fluid, requiring from 15 to 20 drops of cerebrospinal fluid to turn 5 c.c. of Uffelmann's reagent to a canary yellow. Acetone bodies were negative in all of the fluids. The H-ion concentration ranged from 7.4 to 7.6 in terms of pH when the fluid was examined immediately after withdrawal from the body. On standing the H-ion concentration of the fluid changed rapidly toward the alkaline side, reaching a pH of 8.1 to 8.3 in from five to twelve hours after removal. The alkaline reserve ranged between 36 to 63 per cent. of carbon dioxid bound by the cerebrospinal fluid at 760 mm. barometric pressure and zero temperature, the greatest number varying between 45.7 and 63 per cent., the same as in fluid from cases presenting no signs of meningeal irritation. The changes in cerebrospinal fluid in various diseases cannot be generalized, as each disease presents some changes peculiar to itself.

Classification of cerebrospinal fluid changes must take into consideration qualitative as well as quantitative changes. Meningism, meningitis, and systemic disturbances produce changes in the cerebrospinal fluid. The meningismal changes are an increase in pressure and amount of the fluid, with occasional cytologic and chemical changes. There is no evidence of acidosis. The mode of production of meningism is mechanical, being due to an increase in the blood-pressure within the cranium. The changes in the cerebrospinal fluid of various forms of meningitis differ from each other not only bacteriologically and cytologically, but also physically, chemically and physicochemically. The cytologic, chemical, and physicochemical changes in the various forms of meningitis are both quantitative and qualitative. The H-ion concentration of the fluid of suppurative meningitis is often increased. The H-ion concentration of the fluid tuberculous meningitis runs parallel to that of normal fluid. One of the indications of the presence of a meningitic process as distinguished from the meningism is the presence of sediment in the fluid. The systemic changes in cerebrospinal fluid are encountered during the course of systemic diseases and manifest themselves in an increase of certain chemical elements of the fluid, such as the chlorides in nephritis and sugar in diabetes. The various types of changes in the fluid can be used for the diagnosis of the various diseases. A useful diagnostic means for the differentiation between the various types of meningitis is the behavior of the fluid toward various precipitants such as alkaloids and metallic precipitants.

**Results of Some Experimental Work with Sodium Cacodylate on Athreptic Infants.**—CLARKE and DOW (*Am. Jour. Dis. Children*, April, 1920) define athrepsia as a condition of insufficient nutrition where the infant either fails to gain or where the gain in weight is so slight as to be almost negligible. It is most frequently seen in institutions where many babies are housed. Manipulation and variations of diet make very little change. Arsenic was thought of by one of the writers as being the drug most capable of bringing about a physical improvement and a gain of weight. Dawes and Jackson in a series of experiments in animals concluded that after the injection of sodium cacodylate, arsenic in inorganic form was found in the tissues of the body. They also noted that after the experiments there was almost invariably a gain in weight. The authors selected six infants for study. These were all athreptics. Eight injections were given. Four days intervened between each. These were all intramuscularly or hypodermically and the dose varied from  $\frac{1}{4}$  to  $\frac{3}{4}$  grain as the initial dose, depending on the age of the infants. The dosage was increased until the youngest received  $\frac{3}{4}$  grain and the oldest 1 grain. The ages were from six to fifteen months. There was an increase in hemoglobin in all the children. One child failed to gain during the period of injections, but after one month had gained one and a half pounds. The gains in weight continued in all after the injections had been discontinued. From this study it is seen that graduated doses of sodium cacodylate injected hypodermically are non-toxic, and that it causes an increase in the hemoglobin and a substantial gain in weight and while the series of cases was small, this preparation may be the means of stimulating the athreptic infant to take on weight, and possibly enables him to assimilate his food more readily.

## OBSTETRICS

UNDER THE CHARGE OF

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**The Tolerance of Freshly Delivered Women to Excessive Loss of Blood.**—WILLIAMS (*Am. Jour. Obst.*, July, 1919) caused the blood lost at labor by various patients to be collected and measured and an effort was made to find out what might be taken as the average and physiological loss. In the literature various estimates are given, Barnes stating that one pound is usually the quantity, Tucker 300 c.c., Ahlfeld 800 c.c. When the question of actual hemorrhage is concerned this is supposed to vary from 300 to 1000 c.c. Williams' series was in 1000 consecutive spontaneous labors occurring in 1339 obstetrical patients. Operative cases and premature labors were not included. The blood was collected by placing a sterile douche pan beneath the patient immediately after the birth of the child and after the placenta had been delivered, any blood contained in its membrane was allowed to escape into the pan and the entire quantity then poured into a gradule and accurately measured in cubic centimeters and entered in the history. In this way contamination by amniotic fluid was avoided and the entire amount of blood which escaped during the third stage of labor and after the expulsion of the placenta, was collected and measured. This simple method was satisfactory and fairly accurate. The placenta was delivered by palpating the uterus gently but avoiding massage unless the uterus was boggy or bleeding was excessive. After from five to thirty minutes it was noted that the uterus had risen 4 to 6 cm. above its original location, while in some cases an indistinct swelling appeared just over the symphysis, this indicated that the placenta had become separated, had passed from the uterine cavity and was free in the lower segment or upper part of the vagina. At this time the placenta was expressed by a gentle push on the fundus. Routine massage of the uterus was avoided and so were premature attempts to express the unseparated placenta. The typical Crede method was only employed when there was serious bleeding or when the placenta had failed to separate within one hour after the birth of the child. In 1000 cases the placenta was expressed from the vagina in 973; expressed by the typical Crede method in 18 and born spontaneously in 9. In no case was it removed manually. The average time elapsing between the birth of the child and expulsion of the placenta was 16.3 minutes, the most frequent time for the delivery of the placenta is between ten and fifteen minutes after the birth of the child. The average bleeding was 343.7 c.c. with the extremes varying from zero to 2400 c.c. In two patients the placental period was entirely bloodless. It must not be understood, however, that this average loss gives a correct idea of the amount of bleeding in spontaneous labor as in 527 out of the 1000 cases the amount was less than 300 c.c. The most usual loss is between 100 and 300 c.c. and the reason for the higher average in the series was the inclusion of

relatively rare case of previous hemorrhage. These results resemble closely those of Tucker and Champneys 300 to 360 c.c. and smaller than some others 500 to 800 c.c. In the last, 2058 cases studied by Ahlfelt the average loss was 505.1 c.c. which was 161.4 c.c. or one-third greater. As Ahlfelt practices extreme conservatism in delivering his placenta it would not seem that loss of blood is lessened by such conservatism. To determine the limit of physiological bleeding and postpartum hemorrhage, 600 c.c. was taken, and 130 cases, or 13 per cent., had this loss or more. Experience has shown that serious symptoms do not follow hemorrhage of less than 1000 c.c. but in the series there were 49 women who lost one liter or more; of these, 31 lost between 1000 and 1250 c.c. and 18 more than that quantity; only one patient in the first group showed symptoms of acute anemia, while the second group of 18 were especially interesting on account of the greater loss of blood. The study of the 49 hemorrhage cases in which the loss of blood was 1000 c.c. or more shows similar points of interest. It is generally believed that patients suffering from serious hemorrhage show rapid and small pulse, shock, air hunger, rapid decrease in percentage of hemoglobin and number of red cells, which reaches its lowest point by the third day and then gradually returns to normal. When the histories of these patients are studied they show that not a few women recently delivered may lose excessive quantities of blood without presenting evidence of shock and that occasionally the extent of the hemorrhage would not have been appreciated had the blood lost not been collected and measured. Of 31 women who lost between 1000 c.c. and 1250 c.c. only one showed symptoms attributable to loss of blood. She was considerably shocked and had a pulse-rate of 118 one hour and a quarter after delivery. Four of the 18 losing from 1250 to 2400 c.c. gave some anxiety, but none were seriously ill and all recovered. The condition of the pulse was studied in the 1000 cases during the forty-eight hours following labor, in the group having no hemorrhage the average was 98.66, while in the group having hemorrhage the average pulse-rate was 96.45, a difference of only five beats. Comparing these with patients delivered by operation, it was found that many operative cases had average pulse-rate of 101.9, although they had no hemorrhage. From these figures it is concluded that the pulse-rate following normal spontaneous labor is higher than has been generally believed and postpartum hemorrhage causes less disturbance of the pulse than is generally taught. While the strain of difficult labor necessitating operation causes a greater average elimination than postpartum hemorrhage, in spontaneous labors the average pulse-rate is increased only about five beats when hemorrhage occurs. In operative cases without hemorrhage the normal rate is increased ten beats. The model pulse-rate is smaller than the average. There was a lack of correspondence in the character of the pulse with the quantity of blood lost in cases that had hemorrhage, and this is also true of the general condition of the patient, for in one patient who lost 2400 c.c. of blood the general condition seemed to be good although blood-pressure fell to 70 immediately after labor and the hemoglobin fell to 38 per cent. on the third day. In 5 of the cases of severe hemorrhage a marked reduction in the hemoglobin had occurred, in some of these there was rapid return to normal, but in others the low percentage persisted throughout the patient's stay in the

hospital. The hemoglobin was not markedly lowered unless the hemorrhage exceeded 1250 c.c. In two patients losing 1350 and 1400 c.c. respectively, it fell to 40 per cent. From these observations it is apparent that a certain proportion of women may lose in labor 1250 to 1500 c.c. of blood with comparative impunity and present such slight symptoms that the extent of hemorrhage would not be detected if the blood was not collected and measured. With the usual data these patients had lost from  $\frac{1}{4}$  to  $\frac{1}{2}$  of their total blood. In males and non-pregnant women such loss would produce alarming symptoms, but these were lacking in these parturient patients and transfusion was not considered at any time. The question arises how such immunity is produced and why symptoms of shock do not always develop. It is probable that during the latter months of pregnancy a decided increase of the total amount of blood takes place so that this loss represents a relatively small loss and sufficient is left for the immediate needs of the body. It has been shown by observation that the total amount of blood actually increased during pregnancy, this increase, however, is only slight and the low hemoglobin shown after a serious hemorrhage seems to be proof positive that a large proportion of the blood in the body had actually been lost. We cannot clearly explain these circumstances, but they may be associated with other protective processes which develop during the last weeks of pregnancy and at the time of labor. It has been shown that the nitrogenous metabolism at the time of labor is reduced to a minimum and that women pass through labor with little or no increase in energy consumption as indicated by the oxygen intake and carbon dioxide output. From this it may be assumed that the temporary immunity to the excessive loss of blood some way depends upon these facts and that the patient can get along upon a greatly diminished quantity of blood for a short time after labor so that by the time that normal metabolism has been reestablished the reparative processes will tide the woman over the immediate emergency. It must further be remembered that freshly delivered women are not entirely immune to excessive hemorrhage, but it is interesting to note that the average normal woman can lose 1250 to 1500 c.c. of blood with little or no ill-effect and that many can lose much more with relative impunity. However, in 1 case a loss of 1800 c.c. brought the patient's life into the greatest danger and fatal results have been reported when the loss barely exceeded 300 c.c.

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**Pregnancy and Grippe.**—In the *Arch. mens. d'obst. et de gynéc.*, January 19, 1919, PELLISIER gives an account of an epidemic of grippe in the Tarnier Clinic in Paris. There were 75 patients there pregnant, or in the puerperal period, who were attacked by grippe. The epidemic was preceded by isolated cases, commencing in June, 1918. In two months the number of cases had increased and the diseases had taken on a particularly severe form, the epidemic becoming worse in the month of October. Then it abated in November and December, returning in February and March with considerable severity. When the epidemic was studied it was found that among pregnant and puerperal women that the grippe took almost exclusively the pulmonary form. The mortality was comparatively high, 22 per cent. The grippe condition was aggravated by the intervention of pregnancy and later brought on

pulmonary and cardiac lesions and increased the virulence of the phenomena by intoxication. Infection of the genital tract was very frequent by grippe. The secretion of milk did not seem to be delayed by the disease. Hemorrhage was not especially more frequent either before or after labor. The course of labor and delivery was not changed by grippe. Where asphyxia developed in the mother the forceps was used to prevent her from making violent efforts at expulsion, but these forceps deliveries did not seem to be more frequent than usual in cases of grippe. Twenty per cent. of the cases aborted and 77 per cent. had premature labor. The morbidity and mortality of the children was considerably influenced by the disease. There were twenty-seven born prematurely from the seventh to eight and a half months, and with them the mortality was 52 per cent. None of these children born living and taking the disease survived. Of children born at term the mortality was 25 per cent. and 10 per cent. of those born living and taking the disease recovered. In infants from one to six months old the mortality was 40 per cent., and of those children who became ill and recovered there were 20 per cent.

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**Influenza in Pregnancy.**—ANDERODIAS (*Revue mens. de gynécol. et d'obst.*, June, 1919) had an opportunity to study 29 cases of influenza in pregnant women and among these pregnancy was noted in 37.9 per cent. This corresponds very closely with the statistics of the epidemic of 1889 and 1892. Abortion or premature labor made the patient worse. There was no tendency to bleed and viability had been reached in 61 per cent. of the children. The death-rate among the 29 women was 34 per cent. HARRIS (*Jour. Am. Med. Assn.*, 1919, No. 72) publishes the results of the study of 1350 cases severe enough to have medical treatment. Very mild cases often were not seen by physicians, and in very early pregnancy the diagnosis of pregnancy was frequently not made. In one-half of the pregnant women pneumonia complicated the influenza, and among these the mortality was about 50 per cent., being greater during the last three months of pregnancy. Among all cases the mortality was 27 per cent. When there was no pneumonia the interruption of pregnancy occurred in 26 per cent. and when pneumonia was present in 52 per cent. In the fatal cases the pregnancy was interrupted in the majority (62 per cent.), while in the remaining 38 per cent. there developed abortion or premature labor. When the pregnancy was uninterrupted the mortality was 16 per cent. and when the pregnancy was interrupted 41 per cent.

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**Ileus in Pregnancy.**—TUXEN (*Hospitalst., Copenhagen*, August 6, 1919) has collected in the literature of the subject 106 cases of ileus among parturient or pregnant women. He has personally seen three. One was caused mechanically by torsion of an ovarian tumor. One occurred in a multipara, aged forty-one years, who had given birth to her fourteenth child. Four and a half hours afterward symptoms of this condition developed and at operation a dermoid cyst ruptured was found. The escape of its contents had produced irritation, and this caused ileus. With the third patient the pressure of the pregnant womb at six months had incarcerated the bowel and a few days after operation the uterus expelled its contents.

**The Treatment of Extra-uterine Pregnancy After the Fifth Month.**—BECK (*Jour. Am. Med. Assn.*, September 27, 1919) has studied the records of 262 cases of ectopic gestation after the fifth month. These were observed between the years 1809–1919, and thus include the results of operation before and after the adoption of asepsis and antisepsis. It is thought essential that all these cases were carefully reported, because mortality has usually been high. When the child is viable a relatively large number survived operation, and so the life of the child cannot be disregarded. The best time for operation is during the last month, and if the patient be kept under observation there is very little added risk in delaying until the thirty-eighth week, when the child has the best opportunity for survival. Before operating preliminary preparation for the treatment of hemorrhage should be carried out. It is desirable to remove the placenta if possible, but as this is often difficult and dangerous the case must be carefully studied to determine the best method of procedure. Favorable conditions for removing the placenta are its attachment by a pedicle, which can be ligated with easy exposure of the ovarian and uterine extremities of its blood supply. There must also be easy exposure of the ovarian extremity of its blood supply of the side involved, and the operator must be able to get at the uterus from the opposite side to perform hysterectomy if necessary, thus effecting ligation of the uterine end of the placental blood supply. Before attempting to remove the placenta the vessels supplying the placental site must be ligated, and if this cannot be done the placenta must be left in the abdomen. A retained placenta will ultimately be absorbed, and so when hemorrhage and infection are absent and the placenta cannot be removed the abdomen should be closed without drainage. There is a slight danger of secondary hemorrhage and also infection from the adjacent intestines, and these complications may require a second operation. Should pus form, drainage through the vagina should be instituted. When the removal of the placenta is contra-indicated and the presence of infection requires drainage, or when hemorrhage necessitates the use of a tampon marsupialization should be practised. It is advantageous to employ the continuous use of drainage, as it lessens infection. The writer does not mention the old method of leaving the placenta in the abdomen, stitching the membrane to the edges of the abdominal wall and pack either cavity with sterile or antiseptic gauze. While this may be a somewhat clumsy method it has given good results in many cases, and is less dangerous than the attempt to remove the placenta or leave it behind.

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**Prenatal Care Propaganda.**—LARSON (*Am. Jour. Obst.*, September, 1919) publishes an account of methods of bringing prenatal work in the interest of the public and of the profession. All possible efforts should be made to disseminate accurate information by proper books, lantern slides, motion pictures, posters or panels and by suitable addresses. The interesting example is quoted of King, of New Zealand, who succeeded in securing influential friends and opened the first maternity clinic in the area of choice residence property in the capital of New Zealand.

## GYNECOLOGY

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**Erosive Vulvitis.**—The disease of men known as erosive and gangrenous balanitis has been recognized for several years but the same disease occurring in women as erosive and gangrenous vulvitis is not generally recognized. Three cases of this disease have come under the charge of DRISCOLL (*Arch. Derm. and Syph.*, 1920, i, 170) and he has successfully isolated the etiologic organisms in each case. The predisposing causes seem especially to be filth and prostitution, with attending frequent copulation and exposure, and unnatural sexual relations. All three of these women were inmates of a jail and all had been convicted for prostitution. The diseased genitals were extremely dirty, with a large amount of discharge from the focus as well as from the vagina, and presented ideal conditions for the growth of the specific organisms. In each instance there was extensive ulceration of the part with a slight amount of local edema. Two of the cases presented an inflammatory involvement of Bartholin's gland, while the third gave a history of such an involvement two years before. The most severe case of the three presented an almost complete destruction of the vulva. The labia and clitoris had completely sloughed away, leaving a slit-like ulcer between the legs, with the vagina and anus quite similar in appearance at their outlet, presenting a depressed area in the slit. The ulcer itself extended from the base of the clitoris anteriorly, to the tip of the coccyx posteriorly, and laterally on each side as far as the outer limits of the labia majora, which had completely sloughed off except for a short distance just posterior to the mons, where they projected backward to about the anterior margin of the vestibule. Bartholin's glands had been totally destroyed on both sides. In all the cases the inguinal lymphatics were involved, being moderately enlarged but not suppurating. Local pain and discomfort with violent itching seem to be constant factors and the disease is essentially a chronic process. In all the cases the Wassermann reaction was negative and there was no response to anti-syphilitic treatment, but in each case the characteristic spirochete and fusiform bacilli were isolated from the serum of the ulcers.

**Problem of Uterine Cancer.**—During the last few years there has been attracted to the Woman's Clinic of the University of California Hospital—in large part because of their work with radium—an ever increasing number of cases of cancer of the uterus, according to LYNCH (*California State Jour. Med.*, 1920, xviii, 47), and he feels certain that no one could study the data offered by this mass of material without



concluding very definitely that the general profession is doing little to improve the cancer situation, and that this disease in the hands of men doing surgery is quite as hopeless as it was years ago when MacMonagle reported his series of 481 hysterectomies for uterine cancer with only two ultimate cures, and when Baldy confessed that he had never cured a case by any form of treatment. Lynch states that there is no doubt but that we may not attain a proper solution of the cancer problem until the laity is educated to appreciate the importance of the earliest symptoms. Yet such education will avail but little a patient who falls into the hands of one who has not yet recognized the essentials of proper treatment and Lynch believes that we will make greater headway in our problem by devoting our chief effort at present to the physician rather than to the layman, since the physician has long been led afield by a mass of conflicting literature. A large part of the confusion in the literature has developed because the earlier student of cancer grouped in his investigations cancers from all parts of the body, ignorant of the fact that cancers differ markedly among themselves. In the same manner our gynecologic literature teems with contradictory statements because so many have grouped together in their study all cancers of the uterus, which differ so markedly among themselves in their habits of growth. Cancer of the cervix constitutes the problem of uterine cancer because so few are cured. In comparison with cervical cancers, carcinomata of the body lose their importance since they usually permit of cure. Leucorrhea and hemorrhage are the only symptoms of operable cervical cancer. Yet we are constantly disappointed in finding that many cases are frankly inoperable even though they present themselves for treatment shortly after the first sign of bleeding. There is, however, a clear reason for this fact. Only about one-tenth of the cervical cancers are everting in type, and thus capable of giving early symptoms from bruising of the growth. In the other nine-tenths, the growth early inverts or infiltrates and thus has but little chance to bleed until it has extended sufficiently far out to permit of slough of the older areas which have been deprived of the necessary circulation. Moreover, with the advent of the first hemorrhage, the case is complicated by the presence of an infected ulcer so that we can clearly see that if we await the development of bleeding that we may not hope to cure in the mass of cervical cancers. Hope lies only in the recognition of leucorrhea as the only safe early sign, and prophylactically, in the early repair of cervical lacerations and the proper treatment of gynecologic disease, since cancer is practically unknown in women who have not born children or who have not had some pelvic disorder. Out of the myriads of cancer articles has just come the now accepted truth that we are justified in surgical measures only when they are most extensive, and that all operations should be restricted to early cases. The large remainder of cases are better treated by radium. Experience is teaching us daily that if there is question as to operability, the case does not permit of cure by surgery. Experience with radium convinces Lynch that early growths are best treated by extended removal, and all others by radium, which has no equal as a palliative measure. Whether radium cures or not may be an open question, but nothing treats so successfully a case which does not permit of an extensive operation.

**Toxicity of Pyelographic Media.**—A recent death in the Mayo Clinic following pyelography for which a solution of thorium nitrate was used led WELD (*Jour. Urology*, 1919, iii, 415) to make a study of the toxicity of the different pyelographic media. As a result of his experimental work along this line on dogs, he concludes that potassium iodide should be used with great care as a pyelographic medium because of its toxicity and because of the fact that it is readily absorbed from the pelvis of the kidney. Death following the use of potassium iodide is very evidently due to the potassium radical, since sodium iodide produces very little effect. At least one of the toxic effects of thorium nitrate is on the heart muscle, as may be shown by the fact that cardiac failure follows the administration of thorium nitrate even after section of the vagi and the administration of such drugs as nicotin and atropin. Thorium nitrate seems to vary in toxicity according to the age of the solution, possibly because of the conditions under which it is kept. Unfortunately, sodium or potassium iodide, when used in the renal pelvis and bladder in man, often causes considerable local irritation in a solution of 20 to 25 per cent. as originally recommended. Sodium bromide is non-toxic, cheap, easily prepared, readily accessible, non-irritating, and would seem to be the best medium yet brought forward and the author advises a 20 per cent. solution for pyelography, while a 10 to 15 per cent. solution is sufficient for cystography. The drug should be chemically pure and the solution should be sterilized by boiling before it is used.

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## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**The Pigmentation of Nerve Cells; the Lipochrome a Plant Carotinoid Pigment.**—It has been shown that the natural yellow pigments in the cow and hen originate from carotin and xanthophyll pigments in food. Those species, as the cow, horse, hen and man, whose tissue fat is colored with carotinoids, carry the pigments in the blood serum, while those in which the tissue fat is colorless, as the rabbits, dog, swine, sheep and goats, carry insignificant traces of carotinoids under the most favorable conditions. Further, the rabbit and dog have colorless fat and show no lipochrome, while man and cattle, which have colored fat, do. DOLLEY and GUTHRIE called attention to the production of a melanin pigment in nerve cells by functional depression, the pigment being absent normally and having its histogenesis from nuclear material. The present work (*Jour. Med. Research*, 1919, xl, 295) deals with the presence of lipochrome, fat-holding or fat-combining pigment in nerve cells under certain conditions and in certain species. It has been demonstrated that the yellow pigment of egg yolk and blood serum of the hen is a

xanthophyll and that, while white leghorns fed continuously on a carotinoid-free diet from birth, lay colorless eggs and are all but entirely devoid of pigment, the color rapidly appears upon administration of a carotinoid diet. To demonstrate the relation of carotinoid pigment feeding to nerve cell lipochrome, twelve chickens were studied. Six were made carotinoid-free, and six carotinoid-full, while in three of each group, the factor of depression was introduced by producing beriberi, exposing to a temperature of 40° to 45° C., or administering morphin or phosphorus. Those chickens which received a carotinoid-containing diet showed the presence of yellow pigment. No lipochrome could be found in the nerve cells of the carotinoid-free chickens. The lipochrome was most abundant in the depressed group. As with melanin, the greatest quantity was found in the Gasserian and spinal ganglia. The identity of the microchemical reaction of the lipochrome consisted in the ferric-chloride test which oxidizes the pigment and becomes reduced to ferrous chloride, so that the oxidized pigment loses its color and the red ferric chloride changes to a vivid green. Lipochromes and lipins may be mistaken for one another or may occur in combination. The identification of lipochrome with carotinoid permits of positive deductions, as there is no more fat-holding pigment than there is pigment-holding fat. Melanin can be separated microchemically from lipochrome by the application of fat solvents, hydrogen peroxide, ferric-chloride, silver nitrate or Nile blue. The authors believe that their results contradict Lubarsch's conception that the fat-holding pigment is a "wear and tear" pigment in nerve cells, pointing out that the so-called metabolic pigment is, in reality, an exogenous one. Melanin, on the other hand, may be conceived, under certain conditions, as an abnormal "wear and tear" pigment, being governed by extracellular agencies.

**The Sterilization of Lipovaccines.**—The substitution of oil for saline solution as a vehicle for bacterial vaccines to immunize against typhoid fever and pneumonia offers distinct theoretical advantages and has recently been rather extensively employed. Unfortunately, certain methods of preparation have not proved wholly satisfactory in that the dependability of the final sterilization has been problematical. Utilizing the results of Loeffler's work, that dry heat will kill bacteria without destroying their antigenic properties, LEWIS and DODGE (*Jour. Exp. Med.*, 1920, xxxi, 169) sterilized pneumococcus and typhoid lipovaccines by heating to 130° C. for three hours or to 120° C. for twelve hours in an electric oven. The pneumococcus lipovaccine was prepared according to the method of Whitmore and Fennel. Control cultures of the unheated vaccine yielded *Bacillus subtilis* and other organisms in the majority of instances. It was shown that *Bacillus subtilis* will remain viable in unheated lipovaccine containing chloretone for months. Both the heated and unheated lipovaccine was administered, subcutaneously in a dose of 0.5 c.c. to healthy mice, and, after varying periods, the resistance of these mice was tested by intraperitoneal injections of multiple lethal doses of pneumococci. It was found that the heat did not decrease the antigenic qualities of the lipovaccine appreciably; that the protection afforded was at least ten times the fatal dose and that the optimum period was thirty-five to thirty-eight days after the prophylactic dose. No protection was gained at twenty-one, fifty-six or one

hundred and ten days, from which the authors concluded that the immunity following a single dose of the pneumococci lipovaccine is slow to develop and transient. Typhoid lipovaccine, similarly heated and unheated, was given to rabbits, intraperitoneally, in a single dose of 1 c.c. The comparison of the agglutinin content of the blood of these rabbits with those receiving three doses of typhoid vaccine in saline solution demonstrated that the antigenic properties of the particular lipovaccine employed was almost destroyed by heating to 130° C. for three hours.

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**Pfeiffer's Bacillus and Influenza.**—WOLLSTEIN (*Jour. Exper. Med.*, 1919, xxx, 555) presents results of a serological study during the recent epidemic. Pfeiffer bacilli were grown on a rabbit's blood agar, blood broth and oleate agar. For serological study, convalescent patient's sera and monovalent immune sera produced in rabbits, were used. Spontaneous clumping of the Pfeiffer bacilli rendered agglutination reaction rather unsatisfactory. The reactions showed a great variation and were inconclusive. Active antigens for complement-fixation reactions were obtained from blood broth cultures of the organisms. Complement-binding bodies were absent from the blood of four normal individuals. Fixation antibodies were present in the blood of influenza patients at the end of the first week, increasing in strength during the second week and had disappeared from the blood stream between the third and fourth month. A complicating pneumonia increased the complement-binding power of the serum. Fixation antibodies were found in immune rabbit sera. Precipitin reactions paralleled the complement-binding phenomena. Two or three c.c. of the filtrates from seven strains of Pfeiffer bacilli, injected intravenously killed rabbits in one or two and one-half hours. The filtrates from other strains were much less lethal. Protection experiments on mice, using sera of rabbits which had been injected with poisonous filtrates were unsatisfactory. Convalescent human sera gave no protection.

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**Grouping of Bacillus Influenzæ by Specific Agglutination.**—The results of immunologic reactions on strains of hemophilic organisms, particularly *B. influenzae*, have varied widely. Some investigators have failed to demonstrate immune bodies, others have established specific agglutination with the homologous serum of a given strain and still others have indicated almost complete absorption of agglutination for both the immunizing and heterologous strains. SMALL and DICKSON (*Jour. Infect. Dis.*, 1920, xxvi, 230) were able by agglutination and absorption tests to place seven of ten strains of *B. influenzae* into two groups. Three fell into group I, four into group II, while groups III and IV contained one strain each. The last strain did not correspond to the usual morphologic characters of *B. influenzae* in that it was very pleomorphic. It was not grouped but was most closely related to the members of group III. Immunization was performed on rabbits. The antigens consisted of saline suspensions from cooked blood-agar plates which had been inoculated with strains isolated from the nasopharynx and bronchi of the human. The agglutination tests showed some cross group agglutinins between group I and II and also between groups III and the unclassified strain and the two groups. The strain termed group IV appeared more strictly unrelated to the others.

## HYGIENE AND PUBLIC HEALTH

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**Conjugal Tuberculosis.**—WARD (*Lancet*, October 4, 1919, p. 606) states that there is considerable difference of opinion in regard to the frequency of conjugal tuberculosis. Probably the most authoritative opinion is that conjugal infection is rare, and any increased incidence is attributed to predisposition and causes other than direct infection. The author as tuberculosis officer of South Devon has visited the homes of reported cases of tuberculosis and examined the patient and the contacts in the home. Out of 156 cases in which husband or wife was examined, 91 (58 per cent.) were found to be tuberculous, 16 (10 per cent.) suspect, 49 (32 per cent.) negative. Considering wives whose husbands were first reported, out of 120 cases, 66 (55 per cent.) were tuberculous, 12 (10 per cent.) suspect and 42 (35 per cent.) negative. Among husbands of tuberculous wives, in 36 cases, 25 (69 per cent.) are tuberculous, 4 (11 per cent.) suspect and 7 (20 per cent.) negative. During the five-year-period in which the figures were collected the tuberculous mate first reported has died in 15 cases, and in 7 cases both husband and wife have died. Comparing the results with contact other than husband and wife, out of 1057 examined, 219 (20 per cent.) were tuberculous, 284 (27 per cent.) suspect and 566 (53 per cent.) negative. Considering the contacts of cases examined and found non-tuberculous, out of 81 examined, 4 contacts (5 per cent.) were tuberculous, 7 (8 per cent.) suspect and 70 (87 per cent.) negative. A statistical study of this kind is open to many criticisms. However, the figures have all been collected by one observer and hence may be justly compared. They were collected in the course of everyday work and not for the purpose of proving or disproving any theory. After following up these cases the author is convinced that the great majority of the mates of tuberculous husbands or wives do sooner or later show signs of tuberculosis, but also that the great majority of those infected recover, and recover more rapidly than ordinary tuberculous patients. This may be attributed to an enhanced immunity conferred by graduated doses of bacilli. Over 50 per cent. of all cases of tuberculosis are due to direct personal infection, and for that reason highly infective cases should be isolated.

**Ivy and Sumac Poisoning.**—SWEET and GRANT (*Public Health Reports*, 1920, xxxv, 443) give a discussion of the whole subject of rhus poisoning. The plants responsible are described, and, following this, the purely medical phases of the subject. The irritating principle

of the plants is toxicodendrol, an oily substance which is widely distributed throughout the plants, the most minute amount of which can produce the characteristic poisoning. The contact may be direct or through an intermediate object, as clothing. The smoke from burning rhus may give rise to the poisoning. The matter of individual susceptibility is very important, many persons being practically immune but developing the manifestations of poisoning after prolonged exposure or intense application. The time between exposure and development of symptoms varies from a few hours to five days, depending on the susceptibility of the person, the degree of exposure and the part exposed. A tub bath may be the means of wider distribution of the irritating principle. The clinical manifestations vary somewhat and are not of special importance, being similar to those of other irritant poisons. Prevention may be accomplished, at least in part, by the use of rubber gloves or ordinary gloves, by washing of the exposed part thoroughly with soap and water, being careful not to disseminate the poison. Diluted alcohol is also useful to remove the irritating material. There is no specific treatment and the irritation is essentially self-limiting, usually disappearing in a week or ten days. For relief of itching immersion in hot water is recommended and exposure to air, rather than bandaging, is advised. A 10 per cent. solution of sodium hyposulphite is useful, as is a 1 to 10 dilution in water of the fluid extract of grindelia. Sugar of lead, so long in vogue, is not advised. The blisters may be opened with a needle. Poison ivy and sumac should be destroyed by plowing and cultivation of the land, by repeated mowing of the plants and by sprinkling of the foliage with kerosene. Arsenate of sodium, in the proportion of 2 pounds to 10 gallons of water, is an efficient spray for use when the ivy clings to buildings and fences.

#### Water-borne Typhoid Fever Outbreak in Tonawanda, New York.

—THEODORE HORTON, Chief Engineer, New York State Department of Health (*Public Health Reports*, 1920, xxxv, 391) presents the following conclusions based on data secured from an outbreak of typhoid fever in a community which had been given ample warning of the risk incurred by using an unprotected water supply. From the evidence presented in this report and in the appended tables, it may be concluded: (1) That the outbreak of typhoid in Tonawanda, herein described, was due to an intensive infection of the public water supply, following the breaking of the intake line at a point in the river considerably nearer the American shore than the intake crib. (2) That had a chlorination plant been installed and in proper operation prior to this outbreak, as had been repeatedly recommended by the State Department of Health, the outbreak would not have occurred. (3) That the installation of a chlorination plant resulted in an almost immediate checking of the outbreak and undoubtedly prevented a much more severe outbreak from subsequent leaks in the new intake line when this line was first put into service. (4) That since its installation the chlorination plant has been operated with care and efficiency. (5) That most, if not all, of the local wells in the city of Tonawanda undoubtedly receive gross pollution; and in the case of the Johnson well, it is probable that actual infection occurred. (6) That at certain mills the accessibility of polluted industrial water supplies and their

consequent use for drinking purposes, either through ignorance or carelessness, give opportunity for infection of employees. (7) That while chlorination, if properly supervised, will greatly minimize the danger of infection from the public water supply, it will not improve the physical quality of the supply; and, in the case of the Tonawanda supply, which is at times decidedly turbid, filtration is necessary to produce a supply of a satisfactory physical quality at all times.

**Occupation in Relation to Tuberculosis.**—KOBEL (*Public Health Reports*, 1920, xxxv, 751), after a consideration of some of the general features of his subject, deals with the general subject of indoor life, and points out that by providing ventilation and sufficient space the disadvantages of indoor existence may be overcome. Occupation has marked influences which must be considered in connection with other factors; thus the mortality among those engaged in agricultural pursuits is 8.71 per cent., among bookkeepers and accountants 22.5 per cent., but among Government officials and bankers less than 8.7 per cent., and among draymen, hackmen and teamsters 23.4 per cent. Among dusty occupations, exposure to hard dusts produces a different kind of lung lesion from other dusts, the former being more severe, but all predispose in some degree to tubercle infection, but here again other important factors of environment must play a large part. Throughout the study paradoxical facts were observed, such as the higher rate among male domestic servants as compared with females of the same occupational group, while the reverse holds true in comparing males and females in manufacturing pursuits and in office work.

**Dried Milk Powder in Infant Feeding.**—Safety, usefulness and comparative value. A preliminary report: PRICE (*Public Health Reports*, 1920, xxxv, 809) fed groups of infants under six months on milk prepared from whole milk powder on that prepared from skimmed milk powder, with the addition of unsalted butter, and, finally, controls on normal grade A milk. The infants were observed over a period of only about three months, but the indications were that the remade milks were satisfactory as infant foods, and indeed, at times, may have points of advantage. The two kinds of remade milk should be labelled to show just what they are and never as natural milk. The tentative conclusions refer to one brand of remade milk only.

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ORIGINAL ARTICLES.

THE BLOOD-SUGAR TOLERANCE TEST AS AN AID IN THE  
DIAGNOSIS OF GASTRO-INTESTINAL CANCER.<sup>1</sup>

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AND

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THE great difficulty arising in the diagnosis of gastro-intestinal carcinoma, especially in the early stages, has long been recognized. In spite of our modern methods of investigation, including the most recent tests, the diagnosis in many instances remains obscure often until late in the progress of the disease and is frequently not revealed until exploratory incision establishes the true nature of the affection. Any additional help therefore which may lead to the solution of this difficult problem cannot but be of the greatest value. In the blood-sugar tolerance test we believe there has been added a further step in advance in this direction.

The fact that a high blood-sugar content is usually observed in patients affected with carcinoma has been known for many years. Freund,<sup>2</sup> in 1885, was the first to point out on the basis of seventy blood-sugar investigations that there is always a hyperglycemia in this disease; on the other hand he was unable to observe a similar condition in sarcomatous patients; he therefore recommends on this

<sup>1</sup> Read at the Meeting of the Association of American Physicians, Atlantic City May 4, 1920.

<sup>2</sup> Allgemeine Wiener med. Zeitung, 1885, No. 9, S. 102.  
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account that blood-sugar estimations be made as an aid in the differential diagnosis between the two affections.

Trinkler<sup>3</sup> investigated the blood-sugar content not only in carcinomatous patients but also in patients affected with other diseases, such as typhoid, pneumonia and tuberculosis. In these observations there were 109 analyses, which were divided into two groups: (1) the estimation of sugar in the blood collected at operation, and (2) in that obtained at autopsy. A far greater hyperglycemia was observed in carcinoma than in other diseases.

The following table of Trinkler is interesting, as it presents the average, maximum and minimum percentage of sugar in the blood as observed by him in various diseases:

	Average.	Maximum.	Minimum.
Cancer . . . . .	0.1819	0.3030	0.1023
Typhoid . . . . .	.0950	.1022	.0875
Lobar pneumonia . . . . .	.0943	.1092	.0813
Dysentery . . . . .	.0838	.0915	.0796
Heart disease . . . . .	.0737	.0897	.0664
Peritonitis . . . . .	.0701	.0917	.0450
Tuberculosis . . . . .	.0652	.0817	.0450
Syphilis . . . . .	.0553	.0748	.0449
Nephritis . . . . .	.0489	.0559	.0311
Uremia . . . . .	.0375	.0559	.0311

Trinkler arrived at the following conclusions:

1. Hyperglycemia is always present in cancerous patients.
2. In carcinoma of the internal organs there is always a far greater hyperglycemia than in carcinoma of the skin or mucous membrane.
3. The cachexia of carcinomatous patients bears no relation whatever to the increase in blood-sugar.

In recent years many important investigations have been published by various observers regarding the significance of alimentary hyperglycemia as a test of sugar tolerance in health as well as in disease.

Jacobson<sup>4</sup> was the first to point out the importance of such investigations. He presents his results in 14 normal individuals following the administration of 100 gm. of glucose, and observes that an increase in blood-sugar occurs within 5 minutes after the administration of the glucose rising to its height in 30 minutes, which is followed by a gradual decline to the normal level in approximately 120 minutes, the blood-sugar increasing thus from 0.10 per cent. to 0.22 per cent. in 30 minutes and then gradually falling again to 0.12 per cent.

Hopkins,<sup>5</sup> working along similar lines, observed in his investigations that in health a moderate rise in blood-sugar (0.11 to 0.156 per cent.) occurs after the ingestion of 100 gm. of glucose reaching

<sup>3</sup> Centralblatt f. die medicinischen Wissenschaften, 1890, No. 28, S. 498.

<sup>4</sup> Biochem. Ztschr., 1913, S. 411.

<sup>5</sup> AM. JOUR. MED. SC., 1915, cxlix, 254.

its height in from 30 to 120 minutes, and again quickly subsiding. He also notes that hyperglycemia is most pronounced in certain diseases, as in diabetes, pancreatic, nephritic and pituitary cases, in pneumonia, apoplexy, typhoid, tuberculosis and cancer.

A very elaborate and careful study of alimentary hyperglycemia has been published by Hamman and Hirschman.<sup>6</sup> These observers have pointed out that in normal individuals after the ingestion of 100 gm. of glucose the blood-sugar rises to a maximum concentration not exceeding 0.150 per cent., reaching its height in 30 minutes, which is followed by a gradual fall.

Similar observations were carried on in various diseases, *i. e.*, diabetes, nephritis, disturbances of the thyroid gland and hypophyseal functions, with rather definite results, and in some of these conditions rather typical curves were constructed, which are of considerable diagnostic significance.

The first careful investigations as to the glucose tolerance in cancer were published by Rohdenburg, Bernhard and Krehbiel.<sup>7</sup> Sugar determinations were made of the blood just before and again in 45 minutes, and 120 minutes after the ingestion of 100 gm. of glucose. While the normal individual presents an increase in the blood-sugar percentage, reaching its maximum in 45 minutes, which then gradually recedes to the normal, the cancerous patient begins with a normal blood-sugar, rising steadily in 45 minutes after the ingestion of the glucose to 0.18, or 0.2 per cent., and continues to rise or remain stationary for 120 minutes after the ingestion of the glucose, the percentage being either as high as the 45-minute reading or higher, reaching 0.28 per cent. or even to 0.35 per cent. The blood-sugar content then gradually begins to recede, approximating normal in from 180 to 240 minutes. This character of curve was observed in 24 cases of carcinoma and in 1 case of sarcoma, and was not found in other diseases.

According to these observers the sugar tolerance bears no relation to the location of the tumor, for primary carcinoma of the lung, sigmoid, stomach, heart and other organs all present similar findings.

Benedict and Lewis<sup>8</sup> report their observations in the blood-sugar content in 53 patients affected with malignant growths; the blood being taken 180 minutes after the ingestion of food. Of these cases 10, or 36 per cent., revealed a marked increase in blood-sugar, ranging from 0.12 to 0.16 per cent. At least 49 per cent. of the cases showed a tendency to hyperglycemia. According to these investigators there was noted a steady increase in the blood-sugar content as the disease progresses, reaching a maximum just prior to death, the hyperglycemia being in all probability a result of a constant demand of the growing tumor for carbohydrates.

<sup>6</sup> Arch. Int. Med., November, 1917, vol. xx.

<sup>7</sup> Jour. Am. Med. Assn., May 23, 1919, 1528.

<sup>8</sup> New York Med. Record, October 19, 1914, lxxxvi, 650.

Williams and Humphreys<sup>9</sup> observed a moderate increase in blood-sugar in 9 cases of carcinoma after the ingestion of an ordinary meal; they give no determinations following a dextrose meal; these investigations are therefore of but little clinical value. Cammidge<sup>10</sup> also calls attention to the hyperglycemia present in carcinoma, believing that in explanation of this finding there may be at hand a faulty functioning of the endocrine glands for a "similar hyperglycemic response followed by a delayed fall to normal has been observed in hyperthyroidism and exophthalmic goiter." Very recently, and since the completion of our study, Rohdenburg, Bernhard and Krehbiel<sup>11</sup> have published the results of an elaborate investigation on sugar mobilization based upon 228 cases. These authors call attention to three different types of reaction accompanying the sugar-tolerance test: In the first type, termed 1, the blood-sugar at the 45-minute interval rises above the zero hour figure and at the 120-minute interval is as high or higher than the 45-minute interval. In type 2 the rise in the 45-minute interval occurs as in type 1, but at the 120-minute interval the curve falls almost or completely to the original figure. In type 3 the initial sugar concentration is higher than or the same as that at 45 minutes, and the 120-minute interval shows a return to the original figure more or less complete, sometimes going even higher.

In nephritis 75 per cent. of the cases gave type 2 reaction; 60 per cent. of the tuberculous cases gave type 1 reaction; 72 per cent. of the cases of syphilis showed type 2; 60 per cent. of the diabetic type 2 curve; 66 per cent. of the pregnancy cases gave type 1 reaction. These investigators have materially modified their previous views regarding the blood-sugar concentration in cancer. They found that 61 per cent. of gastric carcinomata and 50 per cent. of intestinal carcinomata gave type 1 reaction, and are of the opinion that the high sugar concentration observed in gastric carcinomata is in no way due to cachexia. They do not consider that any of the three types should be considered as diagnostic of any pathological condition, though generally conditions associated with increased cell growth present a greater percentage of type 1 reaction.

The great difficulties arising in the diagnosis of gastro-intestinal carcinomata, especially in the early stages, have led us to make a further study of the blood-sugar tolerance test as an aid in the differential diagnosis between carcinoma and other diseases of the abdominal organs, realizing full well, from the work of Rohdenburg and his co-workers, that a test of this character can serve only as an additional help in diagnosis, but must in no way be considered as specific of any disease.

In order to establish the practical utility of the blood-sugar

<sup>9</sup> Arch. Int. Med., 1919, xxiii, 537.

<sup>10</sup> Practitioner, February, 1920.

<sup>11</sup> AM. JOUR. MED. SC., April, 1920.

tolerance test the method employed must be, though necessarily accurate, so simplified as to be easily carried out and not too time-consuming. In our examination we have followed the plan recommended by Hamman and Hirschman, as well as that of Rohdenburg, of giving after a night's fast 100 gm. of dextrose thoroughly dissolved in 300 c.c. of black coffee without additional sugar. The blood was withdrawn for examination by puncture from the arm vein just before and again in 45 minutes, and 120 minutes after the administration of the dextrose. The blood-sugar was determined by the Epstein method by employing a standardized apparatus which had been thoroughly tested as to its accuracy; we feel that by this method a simple as well as an accurate means is afforded for estimating blood-sugar. The advantages of this method are well known. It requires but 10 to 15 minutes to complete a determination of sugar, necessitating but a very small quantity of blood, and does not entail the employment of an expensive colorimeter, which thus renders the method especially useful for clinical work. Again, the slight error common to our estimations can be of but minor significance, inasmuch as the test is a comparative one of at least three estimations conducted in each individual case, and in addition all of the determinations were made by the same individual under similar conditions. The urine was examined at varying periods in many instances, but sugar was but once observed in any of our cases up to 120 minutes after the ingestion of the glucose; occasionally it was present after 180 minutes.

In our investigations the blood-sugar tolerance was studied in 32 cases of carcinoma of the gastro-intestinal tract. All of the cases were typical of this disease; of these 17 were operated on and the diagnosis was thus confirmed, and in the remaining cases there were definite palpable abdominal masses in addition to the usual physical signs present in this affection; and the examination of the gastric contents as well as the roentgen ray and final outcome presented confirmatory evidence in every instance. Of these cases there were 19 of gastric carcinoma, of which there were 11 with obstruction at the pylorus, 1 at the cardia and 7 presented no obstructions; there were 9 cases of carcinoma of the stomach, with metastases in the liver and other abdominal organs; 2 of carcinoma of the rectum and of the cecum and 1 of the face and tongue. In addition, blood-sugar tolerance tests were made in 3 cases of uterine carcinoma; 1 case of breast cancer; 1 case of carcinoma of the prostate and spine; 1 case of uterine fibroid; 2 cases of sarcoma (1 of the jaw and 1 of the leg); in 8 cases of peptic ulcer; 2 cases of syphilis of the stomach; 3 cases of diarrhea and dysentery; 8 cases of achylia gastrica and chronic gastritis; 4 cases of cholelithiasis; 2 cases of chronic appendicitis; 11 cases of enteroptosis; 5 cases of nervous dyspepsia and 5 cases of intestinal stasis and mucous colitis, making 88 cases in addition to the 4 perfectly normal individuals studied for purposes

of comparison. The sugar tolerance curves as observed in our cases may be classified into the following groups:

1. **The Normal Curve.**—In normal individuals after the ingestion of 100 gm. of dextrose the blood-sugar content rises from 0.09 or

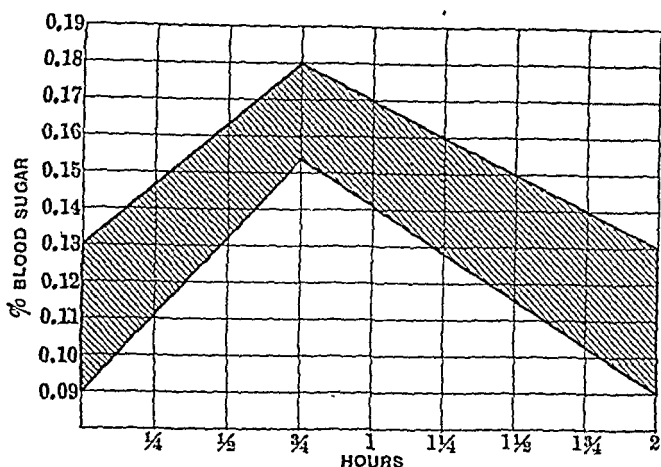


CHART I.—Maximum, minimum and average normal blood-sugar tolerance curve.

even less to a height not usually above 0.165 per cent. within 45 minutes, falling usually more gradually within 120 minutes to about the level as that observed in the fasting state. This character of

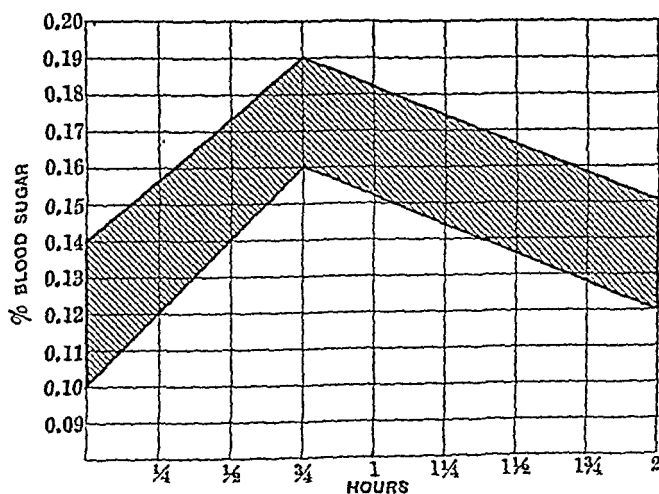


CHART II.—Maximum, minimum and average atypical normal curve.

curve was observed not only in normal individuals but also in the non-cancerous digestive disturbances other than those which have been classified in the following group. The two sarcoma cases also presented normal curves:

2. **The Atypical Normal Curve.** In certain individuals, often those affected with an achylia gastrica, an atypical normal curve is observed in which the blood-sugar content presents practically normal values in the fasting state, ascending to a height of from 0.16

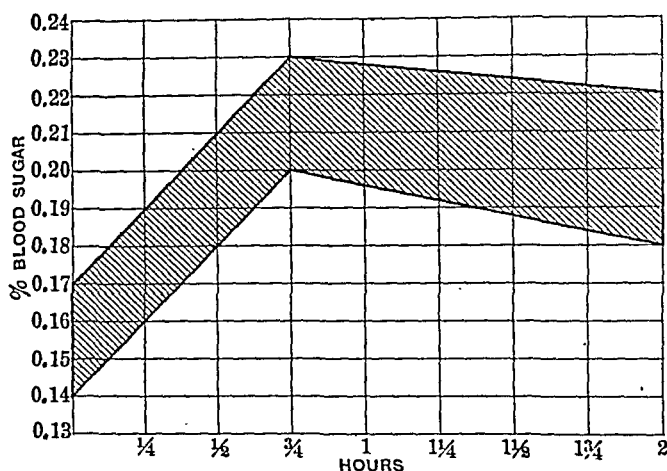


CHART III.—Maximum, minimum and average intermediate blood-sugar curve.

to 0.18 per cent. within 45 minutes after the ingestion of the dextrose, falling slowly within 120 minutes to a level of from 0.13 to 0.15 per cent., but not any lower. This form of curve was found not

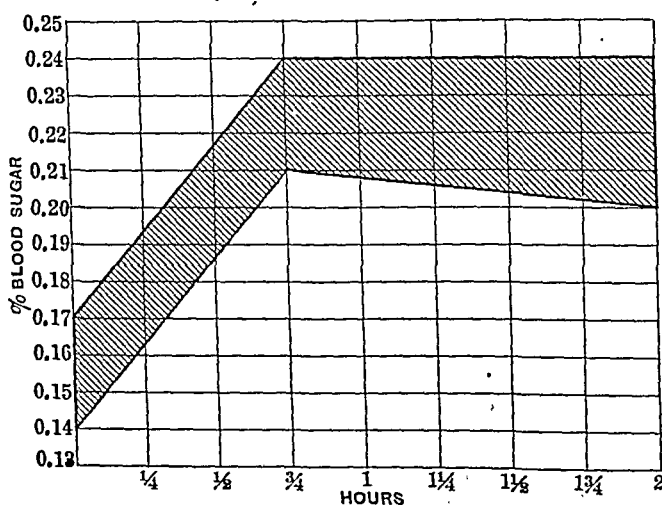


CHART IV.—Maximum, minimum and average blood-sugar tolerance curve in carcinoma of the gastro-intestinal tract.

only in our achylia cases but also in the cases of pyloric stenosis of benign origin.

3. **The Intermediate Curve.** The intermediate curve is usually observed in cases of carcinoma not associated with the gastro-

intestinal tract, in which the blood-sugar content presents comparatively high values even in the fasting state of 0.14 to 0.17 per cent., and in which after the ingestion of 100 gm. of dextrose there is an initial rise to a height of from 0.2 to 0.23 per cent. within 45 minutes, followed within 120 minutes by a fall to a level of from 0.18 to 0.21 per cent., never descending at this time to the level observed in the fasting state. The intermediate curve was observed by us in 3 cases of uterine carcinoma, 1 case of carcinoma of the prostate and spine and 1 case of carcinoma of the breast.

4. **The Cancer Curve.** The cancer curve is usually observed in carcinoma of the gastro-intestinal tract in which even in the fasting state there is a high sugar content of from 0.14 to 0.17 per cent., followed after the ingestion of the 100 gm. of dextrose by an initial rise of from 0.21 to 0.24 per cent. or higher within 45 minutes,

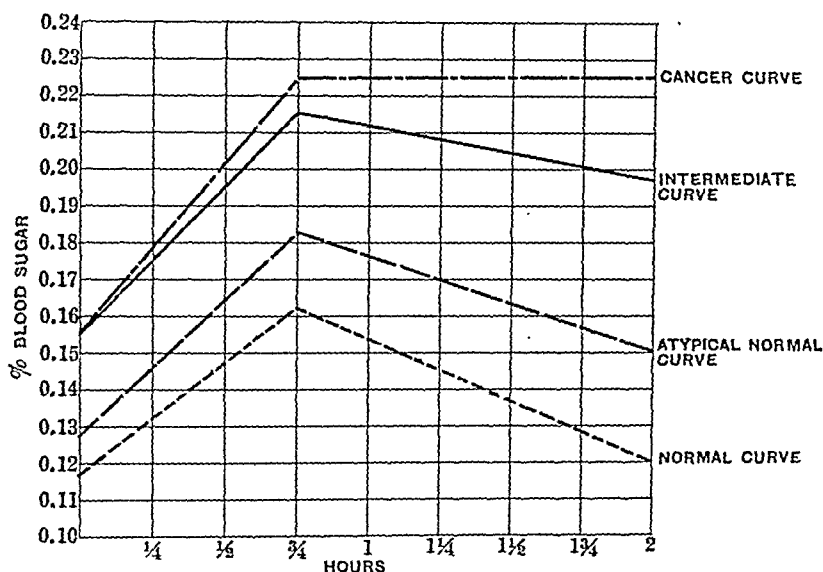


CHART V

remaining at this level for at least 120 minutes, and at no time during this period falling below 0.20 per cent. This form of curve was observed in all of the cases of cancer of the gastro-intestinal tract, but was not present in any one of the other 55 examinations, including 5 cases of carcinoma outside of this tract nor in 2 cases of sarcoma nor in any of the 45 cases of benign affections of the gastro-intestinal tract. The form of curve present therefore in gastro-intestinal cancer is rather characteristic and can usually be distinguished from that observed in cancer of any other region of the body or from that of non-malignant disease. It should be noted, however, that in cases of suspected carcinoma of the gastro-intestinal tract in which the curve is not absolutely characteristic or is of the intermediate type that a second examination made after a short interval of time will usually reveal the true condition.

We have not had an opportunity to observe early cases of cancer of the gastro-intestinal tract according to this test except in a single instance, but we are under the impression that the test is quite as definite in early as in late cases, as it is usually positive whether cachexia exists or not or whether there is but a slight or a marked involvement of the organs. It is important to note that diabetes, nephritis, tuberculosis and disturbances of the thyroid should always be excluded before the tolerance test is undertaken, inasmuch as hyperglycemia is frequently present in these affections. Inasmuch, however, as this test is to be utilized only as a means of differentiation between carcinoma and other diseases of the gastro-intestinal tract, many conditions associated with hyperglycemia need not be taken here into consideration.

TABLE PRESENTING THE PERCENTAGES OF BLOOD-SUGAR OBTAINED  
IN THE 32 CASES OF CANCER OF THE GASTRO-  
INTESTINAL TRACT.

No.	Name.	Cancer of	0 Hour.	45 Min.	120 Min.
1	M. J. B.	Pylorus	0.141	0.250	0.238
2	G. F. B.	Liver and stomach	.12	.198	.192
3	S. S. B.	Stomach	.163	.268	.278
4	T. C.	Liver and stomach	.147	.191	.194
5	G. C.	Liver and stomach	.162	.204	.201
6	M. H. C.	Liver	.196	.240	.243
7	D. E. D.	Stomach	.178	.364	.332
8	C. E. D.	Pylorus and lesser curvature	.131	.187	.183
9	J. A. D.	General carcinomatosis	.161	.258	.255
10	E. G.	Uterus and rectum	.125	.187	.194
11	D. G.	General carcinomatosis	.161	.250	.256
12	H. G.	Liver and stomach	.163	.214	.208
13	W. K.	Pylorus	.149	.198	.194
14	C. S. I.	Cecum	.155	.226	.258
15	P. J.	Pylorus	.142	.187	.179
16	F. L.	Rectum	.202	.300	.264
17	J. L.	Pylorus	.176	.252	.266
18	C. J. M.	Stomach	.158	.210	.210
19	H. C. P.	Stomach	.142	.262	.247
20	G. C. P.	Stomach	.164	.242	.238
21	M. M.	Pylorus	.138	.204	.204
22	R. E. M.	Stomach	.142	.194	.192
23	E. R.	Pylorus	.141	.192	.174
24	I. P. S.	Liver and stomach	.121	.162	.153
25	S. F. L.	Tongue	.384	.497	.497
26	M. S.	Cardia	.131	.180	.224
27	C. S.	Stomach	.206	.266	.256
28	J. T. T.	Pylorus	.171	.239	.240
29	S. V.	Liver and stomach	.139	.214	.206
30	S. W.	Pylorus	.162	.198	.194
31	E. W.	Stomach	.154	.192	.178
32	W. A. Z.	Stomach	.161	.220	.218

The value of the test is well illustrated in three of the cases of this series; we append a brief abstract of the histories of these cases:

CASE I.—M. R. (No. 4857), male, aged fifty-four years, had been complaining of stomach trouble for some months; he was affected with nausea and vomiting; much discomfort after meals



with eructations, flatulency, loss of appetite and loss of flesh (twenty pounds). Recently he had frequently vomited food taken the day previously. On physical examination the liver was found enlarged and there was a definite resistance in the upper right quadrant. The examination of the gastric contents revealed but small amounts of free hydrochloric acid, and there was marked retention. On roentgen-ray examination there was found an enormously dilated stomach, with a large filling defect and a 1080-minute retention. The diagnosis of pyloric obstruction, due to ulceration and possibly to a malignant growth, was made. The sugar tolerance test revealed a normal curve pointing definitely against carcinoma. At operation, performed February 21, 1920, by Dr. J. M. T. Finney, a non-malignant pyloric stricture was found.

CASE II.—E. S. (No. 5002), male, aged forty-eight years, had been affected with indigestion for the past six months. He had lost ten pounds in weight, had nausea, vomiting, loss of appetite and complained of weakness and of the passage of blood in the stools. On physical examination of the abdomen nothing abnormal was determined. His gastric secretion presented a true achylia. The stools contained occult blood and the roentgen-ray revealed a large filling defect at the pylorus, involving a large area on the lesser curvature. The diagnosis of carcinoma was made. The sugar tolerance test, however, presented a perfectly normal curve. At operation, March 1, 1920, by Dr. J. M. T. Finney, a chronic gastritis with pylorospasm was revealed.

CASE III.—M. M. C. (No. 4652), male, aged sixty-one years, complained of indigestion for at least four years, which had recently become more aggravated; there was present loss of appetite, eructations of gas, pressure and fulness after meals, and loss of flesh (twenty pounds). On physical examination of the abdomen the liver was found enlarged; there were no palpable masses present. The gastric secretion presented a low total acidity 10 to 12, with an absence of free HCl. The roentgen-ray examination revealed a large filling defect at the pylorus and on the lesser curvature, on account of which a positive diagnosis of carcinoma was made. The sugar-tolerance test, however, presented an atypical normal curve. The Wassermann test was positive and the patient has recovered after having undergone an antiluetic treatment.

In considering the possible causes that may be responsible for the delayed tolerance curve in the blood in cancer, two possibilities have been suggested by Dr. Charles E. Simon:

1. Whenever increased cell production is maintained there must necessarily be some source of energy available, and inasmuch as the most potent source is dextrose, it is quite conceivable that a special call might be made on the part of the multiplying cells upon the liver for an increased supply of dextrose. Should the liver respond to this call, but owing to the defective blood supply in a carcinoma only a small portion of the available sugar should

be utilized, a hyperglycemia might develop. This hyperglycemia does not occur in sarcoma, which may be explained on the basis that in this disease there is a more or less abundant blood supply, whereas in carcinoma the reverse is observed. The available dextrose in sarcoma would on this account be utilized and a hyperglycemia would consequently not develop.

2. As a second possibility one could conceive that a hormone might be liberated into the circulation by the carcinoma, in consequence of which the normal power of oxidation of the sugar on the part of the tissues at large or of certain special ones, like the muscle tissues, might be impaired; in consequence a hyperglycemia could not only result under normal conditions of carbohydrate supply but also when an increased quantity of dextrose is made available; in addition it might be possible that such a factor might be responsible for the defective nutrition of the body at large and thus for the progressive loss of weight associated with cancer.

From our study of the blood-sugar tolerance test in health, as well as in the various affections of the gastro-intestinal tract, we believe that the following conclusions may safely be drawn:

I. There is present in carcinoma of the gastro-intestinal tract usually a rather characteristic curve of sugar tolerance which differs somewhat from that observed in carcinoma of other regions of the body. The curve of this affection usually presents a high sugar content even in the fasting state, followed by an initial rise up to 0.24 per cent. or higher within 45 minutes after the ingestion of the dextrose remaining at this level for at least 120 minutes, and at no time during this period falling below 0.20 per cent.

II. The sugar tolerance test is rather distinctive, so that it may render valuable assistance in a large proportion of cases as a means of differential diagnosis between carcinoma and other diseases of the gastro-intestinal tract.

III. The opportunity has not been afforded to test a sufficient number of early cases of cancer of the stomach and intestines according to this method, so that as yet the value of this test as a means of early diagnosis has not been established; nevertheless, as positive curves occur equally whether cachexia exists or not, or whether the extent of the involvement be slight or great, we are under the impression that the results may be quite definite even in the early cases of the disease. This question, however, requires further study.

IV. Finally, while we fully realize that this test is not specific of carcinoma and cannot be relied upon alone without entering into the clinical aspects of the disease, and that there are cases of carcinoma in which negative findings occur or non-malignant conditions in which the results are positive, nevertheless we are of the opinion that when properly performed the blood-sugar tolerance test may be of considerable diagnostic help in obscure cases of carcinoma of the gastro-intestinal tract.

**CERTAIN POINTS IN THE DIAGNOSIS AND TREATMENT  
OF PULMONARY TUBERCULOSIS.<sup>1</sup>**

BY LAWRASON BROWN, M.D.,

SARANAC LAKE, N. Y.

At the very beginning of my talk I wish to express my gratitude for the opportunity I have been given to address tonight so many practitioners of medicine. It has become a favorite pastime of a few tuberculosis specialists to berate, to bait, so to speak, the general practitioner, for his ignorance of tuberculosis. If this poor individual has had, for example, under his care two patients in whom not only physical signs but symptoms as well were equivocal, about whom no man without generous funds or a hospital staff at his command could speak authoritatively, and if by chance this maligned worker sends them to different specialists, he may be blamed, by one for even suggesting tuberculosis, for branding the patient, as some put it, with the stigma of tuberculosis when he has not got it, and censured by the other for his ignorance in not recognizing a clear case of tuberculosis. It is sad, but true, that the reputation of many of us depends upon the cook and the indigestion that follow the meal.

Those of you who have read that delightful book, *The Future of Medicine*, by Sir James Mackenzie, who writes at an age when most men dwell in retrospection, will recall what he says of the general practitioner, of his importance in and value to the advancement of medicine. He alone sees disease at its very inception. He discovers the spring, and, as I have said, is often criticized for not doing the impossible, for not determining forthwith into which river it will eventually flow. You have, as Sir James points out, exceptional opportunity of studying disease long before it reaches the consultant, months before the classical picture enables the attending physician in the large hospital to make, without undue mental effort, a diagnosis. Our need today calls less for workers in the laboratory, less for well-trained attending physicians, than it does for trained practitioners who are willing to study carefully, and in detail, symptoms which may indicate eventual disease or may peter out in a state of good health.

The physical signs of all pulmonary disease were worked out by the study of pulmonary tuberculosis. P. C. A. Louis, of Paris, who revolutionized not only our knowledge of tuberculosis but also the method of attacking clinical disease, based his work on a study of only one hundred cases of pulmonary tuberculosis.

It seems then that time spent on so common, on such an uninter-

<sup>1</sup> Read at a meeting of the New York Physicians' Association, New York, March 25, 1920.

esting disease as pulmonary tuberculosis, has borne fruit in the past, and time applied to it today by the general practitioner may even yet reward him as richly in the future as it has done others in the past. I say this knowing full well the enormous energy a general practice consumes, and realizing fully that but a small fraction of us have energy enough for practice and little if any left for such study. I simply wish to place before you the opportunity every practitioner has open to him and not to criticize any of you for failure for one or several reasons in not accepting it.

I shall not attempt tonight to present to you any comprehensive discussion of diagnosis or the treatment of pulmonary tuberculosis, but shall single out here and there certain phases that have interested me.

**Diagnosis.**—The diagnosis of pulmonary tuberculosis, curiously enough, grows more instead of less difficult as time goes on. I can recall the day when a patient with cough and expectoration, and a few fine rales, possibly above the clavicle, was always considered to be suffering from pulmonary tuberculosis. A little later it was pointed out that influenza might produce such a condition, and then for a time we gave all patients admitted to Trudeau, who had never had tubercle bacilli found in their sputum, the subcutaneous tuberculin test. Shortly after this the cutaneous and ophthalmic tuberculin tests were introduced, and if they were of no other help they certainly stimulated the study of the tuberculin reaction. This study and the fact that, given, so to speak, in the dark, tuberculin occasionally set up reactions, which, while never permanently dangerous, were very disagreeable and uncomfortable, led us to use the test less and less. About this time roentgen-ray study of the lungs was introduced, and, as many of you recall, it brought about, first, wonder, then opposition (the opposition of ignorance, if I may so term it), and finally acceptance. Complement-fixation to various specific tuberculous antigens was next added to our armamentarium and helped exclude certain confusing cases. Few of you have not worked at one time or another on some draft board, and most of us appreciate the advance in our knowledge of pulmonary tuberculosis that the study of such large numbers of men has brought about. It has emphasized particularly that chronic tuberculosis may be active and of moment, or inactive and capable of great physical strain without relapse.

For some years we have had sent to us at Trudeau a group of cases that formerly we should have labelled at once "incipient" and dismissed all further thoughts of their diagnosis from our minds. Today more careful study shows that many of these patients have no discoverable pulmonary tuberculosis. Formerly some doubtful cases passed through the institution for the reason that the diagnosis never was but always to be made. To obviate this error we introduced a diagnostic clinic, held weekly, attended by all the staff at

which all data about each patient is presented. This includes a full history, data obtained on complete physical and roentgenologic examinations, sputum examinations (concentrated if necessary), complement-fixation tests for tuberculosis and syphilis, adrenalin test of Goetsch, and tuberculin tests, intradermic and subcutaneous, if deemed necessary. These data, collected largely by different workers, who are usually unaware of the others' findings, are placed upon a blackboard, and are used to determine (1) if tuberculosis infection is present (positive intradermic tuberculin test), (2) if clinical tuberculosis exists, and (3) if the disease is active or inactive, or potentially active, during the first week of residence in the institution.

It seems needless to state that in some cases we can neither affirm nor deny the presence of pulmonary tuberculosis, though rarely do we have a patient who fails to react to the intradermic tuberculin test. I might say in passing that a diagnosis of tuberculosis infection is considered of no moment clinically. We have had to employ and to define various terms. "Non-tuberculous" we have used as implying:

1. No occurrence of tubercle bacilli in the sputum.
2. No persistent moderately coarse rales in the upper chest.
3. No parenchymatous roentgen-ray changes.
4. No history of hemoptysis.
5. No history of pleurisy with effusion.
6. Failure to react to a second subcutaneous dose of 10 mg. of old tuberculin.

If the patient reacts to a subcutaneous dose of tuberculin and has none of the other data, we diagnose him as having "suspected tuberculosis." If some of the data are not obtainable and the remainder negative we call the case "tuberculosis unwarranted."

There is still but one pathognomonic sign of pulmonary tuberculosis, the occurrence of tubercle bacilli in the sputum. Errors, that others as well as ourselves have committed, have led us to believe that one or two or even three tubercle bacilli in a specimen must be confirmed by two observers. We also hold that it is far safer to verify at once by a second examination the presence of tubercle bacilli in the sputum. With the ample facilities afforded today by the private and public health laboratories it is inexcusable for any of us to omit this method of diagnosis. I have been positive from a study of the symptoms and of the physical signs that a patient did not have pulmonary tuberculosis. The roentgen-rays were similarly against it, but tubercle bacilli were found in the sputum on repeated examinations. It will never harm any patient to have his sputum examined as much as it will harm the reputations of some of us to omit it. In many doubtful cases the occurrence of tubercle bacilli in the sputum alone settles the diagnosis. The great emphasis laid upon the occurrence of pulmonary tuberculosis without

tubercle bacilli in the sputum has led in some instances to a neglect of this most important procedure. Tubercle bacilli are often lacking early in the disease when their presence would help us most, and I have seen several cases in which only after extensive involvement of the lung, and only a comparatively short time before death, were tubercle bacilli found in the sputum. Curiously enough the disease may advance in rare instances with little if any increase of symptoms and practically no sputum containing tubercle bacilli. It is of interest to note that in many advanced chronic non-tuberculous pulmonary diseases the chief if not the only point of differentiation is the absence of tubercle bacilli in the sputum. Tubercle bacilli, as you are aware, may be found in the feces and in the stomach content when no sputum can be obtained for examination.

Rales rank next in diagnostic importance to the presence of tubercle bacilli in the sputum. While rales of any description, whether crepitant, fine, moderately coarse, coarse or sonorous or sibilant rhonchi, may and often do, occur in pulmonary tuberculosis, the rale usual in incipient tuberculosis is a moderately coarse rale, depending for resonancy or dulness upon the amount of solidification of pulmonary tissue between the bronchiole or bronchus and the chest wall, heard often only during the rather hurried, somewhat full inspiration that follows a cough. I shall not dwell upon the importance of using a cough in physical examination, for even Laennec called attention to the fact that rales were better heard under such conditions. If after cough you hear no rale be sure to have your patient breathe out half or nearly all of his breath, then cough and inhale as I have indicated. I am sure that all of you are familiar with this procedure. I would like to emphasize, however, one point. Throughout the whole physical examination, and particularly while he is coughing, see that all the muscles are relaxed. If you do not observe this precaution you may overlook rales that are numerous throughout the chest. Too hard a cough may also defeat your purpose. If such rales as I have mentioned are heard in quiet respiration the case has always, in my experience, passed beyond the incipient stage.

The physical examination of the patient has assumed today with the perfection of roentgen-ray technic a position of greater interest and of no less value. The frequency with which tuberculosis early in its course attacks the pulmonary apices, which are, of course, comparatively small in extent and readily susceptible to examination has given physical examination in pulmonary tuberculosis an importance vastly greater for example, than in pulmonary abscess, where extensive pulmonitis may exist about an abscess cavity in the upper or lower lobes, and yet the only physical signs may be some slight change on percussion and distant breathing. It is indeed fortunate for patients that pulmonary tuberculosis so rarely arises and remains localized in the more central parts of the lungs.

However, whatever part of the lung is usually first affected the physical signs most frequently appear first at the apex.

Now the rale to be of significance must occur in the upper part of the lung and must be constant on several examinations. Such apical rales are of greater moment when heard posteriorly to the third vertebral spine than when they occur above the clavicle and in the first intercostal space. Typical rales in a suspicious case rank high in diagnostic import; next, I might repeat, to the tubercle bacilli.

There can be no question that pulmonary tuberculosis can occur without rales, and, indeed, fairly extensive deep-seated disease may exist without any or only with most indefinite physical signs. Symptoms may force a diagnosis of pulmonary tuberculosis, and tubercle bacilli may even be found in the sputum and still no abnormal physical signs occur. It is a common occurrence, I am sure, for many of you to find with a right apical lesion typical rales in the outer fourth and fifth intercostal spaces on the left. These are caused by a deep-seated bronchogenic spread of the disease to the other side. Cases do occur in which only indefinite signs are to be heard for some time, and then suddenly rales appear in an unusual situation and may quickly spread over the whole side. Again I have noticed that as the rales increase some patients become better in every way. The deep-seated disease then may approach finally and quickly the surface of the lung, or at least the bronchi within the area susceptible to stethoscopic investigation contain suddenly an abnormal amount of secretion.

Rales when heard only at the base of one or both lungs should never be considered as due to pulmonary tuberculosis unless tubercle bacilli are present.

Granular breathing, that type of breathing which seems about to break up into fine rales, which suggests that with a cough, rales will be plainly evident (when possibly they may not occur), distant breathing at the right apex, prolonged expiration, possibly high-pitched at the right apex, or high-pitched inspiration, with some roughening or accentuation at the left apex, are among the slighter signs to be carefully noted.

The extensive use of the roentgen ray has been a godsend to many men condemned through ill health to pass their days listening to lungs affected with pulmonary tuberculosis, which through force of circumstances they can never follow to and examine at the end. Here they have a means of repeated autopsies or "shadow biopsies," if I may employ the term. Even if they do fail to reveal some tuberculosis, although in some hands they may be grossly misinterpreted, they have added greatly to the efficiency and accuracy of diagnosis. Take an hour or two off occasionally when you have to go to the radiographer's, and follow him in his interpretation of your plates and others. It is a technic that is just as important for you as that of the laryngoscope or of the ophthalmoscope. I

have no time tonight to go into the details of roentgen-ray diagnosis of pulmonary tuberculosis, but I desire to mention a few of the conclusions that I have reached after prolonged use of roentgen-ray methods.

In the first place you will be asked when you report your patient to the board of health, if he has incipient, moderately advanced or far-advanced pulmonary tuberculosis. This is also required by many institutions if you wish to enter him therein. I am convinced from my observations of the comparisons of many physical examinations and roentgen-ray plates that in a very large majority of cases the roentgen ray shows much more disease than is revealed by physical signs. Recently I have been impressed with the idea that we should replace the term "incipient" by the term "minimal," which implies nothing in regard to time, and everything that we wish in regard to early diagnosis. I have mentioned this for I believe the time is coming when to decide that a patient is really in the minimal stage, roentgen rays must be used, for they show, as I have said, that many of the cases called today "incipient" are really moderately advanced, for we can examine by physical signs only the peripheral portion of the lungs, and unless disease involves this portion it may entirely escape our notice.

In the second place you may be suspicious, on account of slight respiratory changes of an apex, and in no cases does the roentgen ray help more than in these truly minimal cases, where it may reveal a well-marked more or less deeply seated parenchymatous lesion and decide the diagnosis.

In the third place roentgen-ray examination may reveal that the abnormal physical signs are due not to tuberculosis but to some other cause.

I will not pursue this point further but must emphasize that not every radiographer can take plates of the chest suitable for pulmonary diagnosis, and, further, may at times draw conclusions from faulty or excellent plates that seem to me entirely untenable. However this may be, I believe that suspicious symptoms demand not only a carefully physical examination, but a roentgenologic study as well.

Our statistics at Trudeau have been very carefully studied from time to time by Doctor Heise and by some of the rest of us. He has emphasized the importance in diagnosis of two points in the past history of the patient: I refer to the occurrence of hemoptysis, and of pleurisy, which is of more import if associated with effusion. The hemoptysis, of course, must be a dram or more, and is more important diagnostically if followed by streaked sputum for a day or two, or, indeed, if the hemoptysis recurs once or twice. I do not mean to say that streaked sputum is of no moment, for it may be the signboard that suggests the direction of the diagnostic goal. But it does occur frequently in acute bronchitis, and all of you are



aware of the occurrence of frank hemoptysis in pulmonary abscess and more rarely in bronchiectasis.

If our patient has had one of these symptoms we must not only suspect but exclude pulmonary tuberculosis.

I cannot but feel that in all tuberculous pleurisies, with or without effusion, the tuberculosis has gained entrance to the pleura through the blood or lymph vessels of the lung. It is now well known that many small lymph glands and masses of lymphoid tissue are scattered practically throughout the lung, and it is difficult to believe that some tubercle bacilli may not remain behind in some of these lymphoid masses. The experimental work of Patterson and others has proved that tuberculous pleurisy with effusion is always secondary to some other tuberculous focus in the body. In other words, it is the reaction of a sensitized pleura to renewed irritation by the sensitizing agent. It needs but a moment's reflection to conclude that any focus in the body that is shedding tubercle bacilli into the circulation needs our attention at once and demands from us discovery of its location if possible, and in any case careful treatment.

The laboratory furnishes us with many valuable aids, and makes, as I have said, by the discovery of tubercle bacilli, the only diagnosis that is absolutely unquestionable. The importance of the tuberculin cutaneous test in the first few years of life is known to all of you, but in adults no cutaneous, ophthalmic or subcutaneous reaction separates in my opinion active from inactive tuberculosis, or tuberculosis that needs no care from that which demands active treatment. The complement-fixation is positive in the majority of cases, but the fact that 10 per cent. of the patients with tubercle bacilli in the sputum fail to react positively weakens its diagnostic value. It is much like the Widal reaction in typhoid or the Wassermann reaction in syphilis. The clinical data are more important. The repeated absence of a positive complement-fixation test, however, in a case that is only doubtfully tuberculous, and in a moderately advanced stage of disease, lends considerable weight to a diagnosis of non-tuberculous disease.

The determination of the presence of pulmonary tuberculosis does not complete the diagnosis. A positive cutaneous tuberculin test reveals that the patient is allergic and has harbored tubercle bacilli for a time at least in his body. The occurrence of the two symptoms I have emphasized, the presence of abnormal physical signs mentioned, confirmatory roentgen-ray findings decide the presence of pulmonary tuberculosis, even in the absence of tubercle bacilli in the sputum. But here we must solve what is for the patient the crucial point—does he need treatment? In some cases with slight physical and roentgen-ray changes in the lungs we have employed the subcutaneous tuberculin test and studied the lungs for a focal reaction, which occurred in about 18 per cent. when the test was

positive. In all we have given 324 patients the subcutaneous test. Of these 10 have died of tuberculosis and 59 have relapsed in a period covering from two to eighteen or twenty years. In other words, 25 per cent. in whom we were not sure of a diagnosis relapsed and 4 per cent. have died. Of the 42 patients who have failed to react to a second dose of 10 mg. of Old Tuberculin, 2 have relapsed and recovered and 2 have died, 1 from acute lobar pneumonia and 1 from a cause unknown.

As I have come to learn what an amount of disease a chest may contain when the physical signs are equivocal, I wonder that some of these 282 patients were not permanently injured after sharp reactions; but, on the contrary, many felt better, and asked for this reason to be given tuberculin as a treatment. Today we take no such chances, and if the roentgen ray shows any parenchymatous changes they must be very indefinite or else very old and calcified. In our recent cases (numbering 30) we have had 4 only that showed a definite increase of clouding about the suspected areas, and in some of them rales occurred for the first time. Today we send home at once a patient who fails to react to two doses of 10 mg. If he reacts and still shows no change by physical signs or in roentgen ray, we increase rapidly his exercise and send him home in a few weeks if he does well. None of the 42 has ever reapplied for admission, though we have always told them we would take them in at once if they relapsed.

Only a small number of patients can be submitted to such tests, and for many the problem of whether the disease under consideration is active or inactive is not easily solved. We have made some study of it and have attempted to divide the symptoms in relation to activity into two groups: (1) Cardinal symptoms, including hemoptysis, pleurisy, fever, rapid pulse, lack of endurance, loss of weight and night-sweats, and (2) subsidiary symptoms, including chills, cough and expectoration. In our studies we have not considered the presence of tubercle bacilli in the sputum as evidence of clinical activity, though we realize that such patients are much more likely to relapse. We have arbitrarily chosen a temperature of  $99^{\circ}$  F. in the male adult and  $99.5^{\circ}$  in the female, and a pulse-rate of 90 in a male and 96 in a female as the upper limits in non-active cases. Of course, other disturbing factors must be excluded. We studied 198 patients in regard to relapse and found that 90 per cent. of the relapsed had a positive complement-fixation test and that 70 per cent. had been considered "clinically active," while of those who did not relapse 50 per cent. had a positive complement-fixation test and 75 per cent. were "clinically active." The presence of rales was not of much help, and even when they occurred, with tubercle bacilli in the sputum, only 50 per cent. were considered clinically active. The whole subject is very intricate and needs further study, as you can readily see from these figures.

To summarize briefly I feel that fever, rapid pulse, lack of endurance, loss of weight and night-sweats suggest tuberculosis which must be excluded if possible. If to these we add cough and expectoration, which have persisted for several weeks, we must focus our attention for a time on the lungs. But if we can find no more evidence than the symptoms I have just mentioned I do not feel that we can make an absolute diagnosis of pulmonary tuberculosis. To do so one or more of the six diagnostic essentials that I stated in a negative way a few minutes ago must be present. I refer to tubercle bacilli in the sputum (confirmed on two examinations); persistent moderately coarse rales in the upper chest; a parenchymatous roentgen-ray lesion, more weighty if in the upper chest; a history of frank hemoptysis, of pleurisy and a positive complement-fixation test.

Tubercle bacilli, of course, settle the diagnosis. Moderately coarse rales persistent at an apex, more particularly if posteriorly, are nearly as positive as tubercle bacilli unless due to some acute process in the course of clearing up, and then they fail to be persistent. A parenchymatous lesion, more especially in the upper part of the lung, if we can exclude influenza and some of the epidemics seen in the army, ranks a little below the rales described. A combination of rales and a parenchymatous lesion is, of course, more certain than either alone. If to these we can add a history of hemoptysis or pleurisy with effusion the diagnosis can be considered positive. I am speaking now of cases in which tubercle bacilli have never been found. A history of hemoptysis or pleurisy with effusion which cannot be explained by any other cause, in spite of the absence of tubercle bacilli, rales or definite roentgen-ray picture, demands a diagnosis of suspected pulmonary tuberculosis.

The combination of a positive history for hemoptysis or pleurisy with either rales or parenchymatous roentgen-ray lesions demands a positive diagnosis under the conditions mentioned above. A negative complement-fixation test in a patient with moderately advanced disease, without tubercle bacilli in the sputum, bespeaks caution in making a definite diagnosis of pulmonary tuberculosis.

**Treatment.**—Having made a diagnosis of pulmonary tuberculosis and having satisfied yourself that the case needs vigorous treatment, the next step is most important. Pulmonary tuberculosis is a chronic disease. If we exclude miliary tuberculosis, for which there is no treatment with cure as an outcome, even the more acute cases rarely die in less than six months, and, as is well known, the average duration of all fatal cases is between two and three years. The struggle for recovery lasts no shorter time, and if we include relapses, or "setbacks," as our patients call them, extends over a far longer period. In fact, I feel that with many patients the struggle lasts from diagnosis to death, which in at least 90 per cent. of the patients at Trudeau has been caused by tuberculosis.

It is easy to deduce from these facts that a physician must have a sanguine temperament to deal successfully with such a disease, for patient, family and friends all lose courage and grow despondent over the many disappointments that beset the path toward recovery.

Bearing these facts in mind the psychologic treatment of the patient demands careful thought. I do not believe it pays to temporize with the patient. He should be told at once that he has pulmonary tuberculosis. It may come as a shock and nearly prostrate the patient for a while, but you will be the gainer, and in the end the patient will be benefited. He does not and cannot know the difficulties ahead of him, and I doubt the advisability of emphasizing them too much at first. But be sure to tell him enough to gain his whole-souled coöperation. Awake in him, if you can, a fighting spirit. Encourage him or depress him or do both, but from the minute you tell him of the diagnosis assume a strict attitude toward what he should do.

This leads me to emphasize the benefits that many patients derive from proper treatment at its onset, and to call to your attention the "danger time" that the patient passes through at the outset of treatment. I refer to the period of time, usually several weeks, during which the education of the patient progresses to a point where he becomes orientated and aware of the many dangers that follow overexertion. I know of no way more certain to avoid these dangers than to keep your patient in bed on a porch or in a room with wide-open windows until his education has progressed to a point that you feel you can trust him not to overdo. Tell him that he has specks on his lungs like those that occur in apples in March, and that while the apple must necessarily decay in order to liberate the seeds, his lung is constantly forming delicate scar tissue about these specks or tubercles which contain the germs, in an endeavor to wall them off, and, so to speak, strangle the germ in its own juices or excretions. Tell him that at first the scar tissue is so delicate that it resembles spider web and that vigorous or violent respiratory exertions may stretch the delicate scar, liberate some germs which may form new specks or spots which in turn will have to be walled off before he can hope for recovery. In short, say to him that the treatment of pulmonary tuberculosis depends upon two things: (1) the formation of scar tissue, and (2) the protection of the forming scar tissue. The conservation of energy and the conservation of natural resources are familiar to many patients. Tell them rest enables their body to devote more of its powers to form scar tissue and rest of the lungs protects the delicate scars. I try to illustrate this point with my hands.

In recent years I have come to regard rest as the most important point in the treatment of pulmonary tuberculosis. It is far better for a patient to be in bed in a room with fair ventilation for several weeks than to dress and to walk some blocks to a park where he

can sit out for several hours and climb several flights of stairs to regain his room. If you can persuade your patient to do this, seize upon the opportunity to educate him. Put such literature in his hands as he can comprehend and encourage him to write down questions. Tell him frankly that your visits are as important educationally as medically. If you can get him to think out his problem, three-fourths of the battle is won. I usually try to keep my afebrile patients in bed six weeks. Patients with fever demand much longer periods of rest.

Exercise at the proper time is as important as rest, but even then vastly more dangerous. The scar, of course, at the end of six weeks is not densely fibrous and requires careful stretching, such as is exerted by gentle breathing. I do not refer to respiratory exercises, which I seldom use. To reëducate the patient physically requires that the physician should become a physical trainer, who never forgets that he is dealing with a damaged organ that demands far more rest than a normal organ. This, too, must be impressed upon the patient. I sometimes put it that they can play and get well or work and get well, but they cannot work and play and get well. To watch the effect of any new form of exercise, have your patients take it every other day. It has seemed to me that afebrile patients kept in bed six weeks could be given exercise rather quickly. I frequently allow them to take, after they are accustomed to dressing, to going to meals and to climbing the necessary flight of stairs, one-quarter of an hour's slow walking twice a day the first week, one-half the second, three-quarters the third, and one hour the fourth provided, of course, there has been no increase of symptoms. After that if I feel that I can trust the patient I put him on unlimited exercise and tell him never to get out of breath or to get tired. Of course, many patients do not advance this rapidly, and remain at fifteen to thirty minutes twice daily for some weeks. Such treatment as I have just outlined is applicable only to early and favorable cases.

Since the first century of the present era, and possibly before, air or climate has been extolled in the treatment of pulmonary tuberculosis. The oxygen of the air enters the body through the lungs. So air is necessary to the lungs, it has been argued, and bad air would therefore affect the lungs deleteriously. Hence the value of good air for the diseased lungs. Curiously enough the lungs can use and do well in air in which a man cannot live. The value of live, fresh air lies not in its effect upon the lungs, but through the effect upon the body in general. It affects the lungs no more, no less, than the knee. The value of air is exerted in what might be called the air bath. I refer to having fresh air circulate about the patient. It is better, of course, to have him out of doors, but, as I have already said, it is better to be indoors with open windows than overexercising to get fresh air. Window tents that expose the head and neck while

the body is in a warm and possibly badly ventilated room produce the same effect in pulmonary tuberculosis as spraying the face and neck in typhoid fever. Both are good as far as they go, but they stop short of the essential.

Food requirements in pulmonary tuberculosis have undergone considerable change. At first the patient was overfed and now we realize that food has a specific object in this treatment and should be prescribed accordingly. The struggle against pulmonary tuberculosis is a fight to strengthen and to build up the recuperative powers within the individual patients. Scar tissue must be formed. Calcium salts must be deposited. The increased wear and tear of fever, which increases the caloric output of the body by 50 per cent., must be combated. At the same time such patients crave little food. The old idea was that patients needed much meat and milk. It is of interest to note that when after the war an attempt was made to put flesh on some Germans by greatly increasing their fats and carbohydrates it could not be done until an excess of meat was added to the diet. It seems that extra meat is necessary until the patient has a proper amount of protein in his body. If excess of calcium salts are necessary no food furnishes such an amount of this dietary essential as milk, combined, too, probably in such a way that it can be used at once by the body. The fact that the calcium content of the blood serum does not vary in pulmonary tuberculosis is no argument in my mind against its use. One may recall that the same argument was used against the use of iron salts in anemia. Is it not possible that with an increased amount of calcium in the food the blood may pass on to the tissues or scar formation an increased amount of calcium? With a judicious use of milk there is no call for any anxiety about a lack of fat-soluble in the diet of our patients, but it is of interest to note that cod-liver oil and butter fats contain it in large quantities, while all vegetable oils and fats are deficient in it or lack it entirely. The water-soluble B is practically always supplied in sufficient quantities.

In concluding, I should like to state that not every patient in whom a diagnosis of pulmonary tuberculosis can be made needs vigorous treatment. It was an attempt to discover some simple method that any practitioner could use in his office that led us to begin our study of active and inactive cases. We found no simple method. However, my impressions have led me to believe that in considering the need for treatment, symptoms vastly outweigh physical findings in the majority of cases. I frequently tell my patients that the signs the doctor discovers are like the green lights on the railroad, while the symptoms from which they suffer are red lights. A green light means run carefully, and a red light means stop or go on the side track. Tubercle bacilli can, of course, occur in a perfectly quiescent case, that needs follow only a careful life, but when it occurs in a patient who has but recently begun to have

symptoms, vigorous treatment is demanded. Rales, of course, can persist for years in arrested cases. I have seen them apparently unchanged after ten years. The roentgen ray helps greatly in revealing changes that occur from time to time, not discoverable by ordinary methods of physical exploration. But do not forget that an increase of roentgen-ray shadows may occur months before the last plate has been taken, and at that time the patient may have arrested his disease.

Any patient with unexplained pleurisy with effusion needs treatment for pulmonary tuberculosis unless you can exclude definitely any parenchymatous lesion in his lungs, and even then I should incline to the side of caution, for a slight deposit may be lost in the cloudiness that obscures the plate in part at least. An inexplicable hemoptysis should be similarly treated.

Suspected pulmonary tuberculosis we treat by rapidly increasing the patient's exercise to the unlimited stage, and after about three months, if all has gone well, return him to his work.

Finally, we believe that after a careful study the patient can be taken into confidence and frankly told the possibilities—presupposing, of course, that he has some intelligence. Otherwise your final decision must be meted out to him in no doubtful language.

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### ENDOTHELIAL LEUKOCYTES IN THE URINE SUGGESTING TYPHOID INFECTION.

BY O. H. PERRY PEPPER, M.D.,

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Several years ago I reported in this journal<sup>1</sup> a case in which the diagnosis of acute pleurisy with effusion, due to the *Bacillus typhosus*, was arrived at through the finding of endothelial phagocytes in the fluid obtained by pleural puncture. The diagnosis was verified by obtaining from the pleural fluid a pure culture of *Bacillus typhosus* and by the demonstration that both the pleural fluid and the patient's blood serum produced agglutination of known typhoid bacilli.

In the present instance the case to be reported has this point of similarity: that the diagnosis of infection with the typhoid bacillus was reached as a result of the finding of numerous cells which closely resembled the endothelial leukocytes so regularly seen in the various lesions of typhoid fever. In the present instance these cells were found in the urine.

The constancy of the reaction of endothelial leukocytes, using this term in the sense in which it is employed by Mallory, to the

<sup>1</sup> AM. JOUR. MED. SC., 1916, cli, 663.

toxin of the typhoid bacillus, is so marked as to raise a suspicion that the typhoid bacillus is the probable etiologic factor in any cellular reaction in which the endothelial leukocyte predominates, no matter in what portion of the body this occurs. Of course, it must be remembered that the typhoid bacillus is by no means the only organism which brings about an endothelial reaction. Nor is the active phagocytosis displayed by endothelial leukocytes in typhoid lesions peculiar to that infection, although the phagocytic activity may be more marked in typhoid fever than in tuberculosis or in the other conditions in which an endothelial reaction occurs. Furthermore, we must remember that the number and type of cells engulfed by the endothelial leukocytes varies in different regions with the supply and character of cells at hand to be phagocytized.

The observation here recorded may be additional evidence of the universality of the reaction to the typhoid bacillus and of its possible value in the recognition of unsuspected infection with this organism. No more positive claim can be made because of the uncertainty concerning the nature of the cells found in the urine.

The case to be reported is that of a patient who was on the surgical service of the Hospital of the University of Pennsylvania, under the care of Dr. A. C. Wood, by whose courtesy I was permitted to study the case and to make this report.

**Case History.** The patient, a boy, aged sixteen years, was admitted to the hospital on November 7, 1919. His chief complaint was pain in the lumbar region. The history, which was difficult to elicit, and is probably incomplete, was given as follows: On July 4, 1919, the patient took sick and was forced to go to bed. The only symptoms the patient can recall were fever and frequent, painful micturition. The doctor who was called made no diagnosis to the patient's knowledge. The illness kept him in bed for fifteen days, and he was confined to the house for a month.

Subsequent to the illness a pain developed in the left lumbar region which was localized, deep-seated and aggravated by motion. It also seemed to be worse at night, keeping him awake. There were remissions in the pain at first, but after two-and-a-half months, as a result of lifting a heavy weight, the pain became worse and seemed to involve the lumbar spine. Again improvement took place, until six weeks before admission, while playing leap-frog one of his playmates fell upon his back. This aggravated the pain and he was taken to a hospital, where a diagnosis of curvature of the spine was made and he was sent to the University Hospital for treatment.

Since the onset of his present illness he has been somewhat constipated and has had gaseous eructations. His appetite has been poor and he has lost some weight. He has always been a little short of breath and has had palpitation. He did not complain upon admission of any urinary symptoms.



His previous medical history is negative, except for influenza in October, 1918. No venereal infection admitted. He works in a tannery, sorting leather. Otherwise his social history is unimportant. Family history negative.

Physical examination on admission was recorded as negative except for the following statement: "Tenderness alongside the lumbar vertebræ in the muscles. Vertebræ not tender to pressure. Some disinclination to bending spine. Pain also on pressure under left costal margin." On the day of admission the laboratory examinations were: Urine: amber; cloudy; flocculent sediment; specific gravity, 1015; albumin negative; sugar negative. Microscopically: casts negative; cylindroids negative; mucus + +; red blood cells, negative; white blood cells, 1 or 2; epithelium +; triple phosphate crystals.

Blood: Red blood cells, 4,510,000; hemoglobin, 62 per cent.; white blood cells, 9900. Differential count: Neutrophils, 66 per cent.; lymphocytes, 25 per cent.; large mononuclears, 4 per cent.; transitionals, 2 per cent.; eosinophiles, 2 per cent.; basophiles, 1 per cent.

The following ward notes were made.

November 8. Patient complains of more pain in the left side and the back.

November 9. Pain obviously worse; each breath causes pain, and there is some cough. Examination revealed the spinal muscles on both sides in spasm. The right side of the back over the right kidney is markedly fuller than the left. There is impairment to percussion over the base of the right lung, but not much change in the character of the breath sounds.

Temperature has risen to 102°, pulse, 120; respirations, 28.

November 10. Condition unchanged. Temperature fell to normal in morning up to 102.4° by night. Pulse, 112. Respirations, 24.

The patient continued to complain of severe pain and to run an irregular fever, with moderate acceleration of pulse and respiration.

November 13. Leukocyte count, 8000.

November 17. Leukocyte count, 8800. Polymorphonuclears, 57 per cent.; lymphocytes, 35 per cent.; eosinophiles, 3 per cent.

On November 18 I was first asked to examine the patient. The fever and the pain in the back were still the prominent features of the case and physical examination was negative except for the discovery of slight impairment to percussion at the right base posteriorly, with a few faint frictions or rales, but no change in breath sounds. There was tenderness in the iliocostal space on the left side and apparently some spasm of the spinal muscles in this region. An urticaria, probably due to medication, was also present.

A specimen of urine was obtained and found to be grossly cloudy. Centrifugation threw down a whitish sediment resembling pus, but on microscopic examination I found it consisted not of the expected

pus cells but of larger cells, many very large and vacuolated. Their cytoplasm was stained faintly by methylene blue, and, as a rule, there was one large nucleus, though a few cells were seen, with two distinct nuclei. The vacuoles were not present in every cell and varied in number and size. In addition to the vacuoles there were seen in many of the cells round areas of homogeneous appearance resembling fat or hyalin. Some of these took a greenish tint with the methylene blue; none took the fat stains. In a few instances the large cells seemed to contain remnants of lymphocytes, but this was uncertain. It must be remembered that the endothelial leukocytes engulf a variety of cells under different circumstances. In this instance there were apparently no erythrocytes and few other cells available, as no erythrocytes or leukocytes were found in the urine.

The appearance of the large cells strongly suggested phagocytic endothelial leukocytes, and although no suspicion of typhoid infection had been entertained, and the suggestion that these cells might indicate typhoid infection was not taken very seriously, yet it was deemed significant enough for an agglutination test and a culture of the urine to be requested from the laboratory. The report of a positive agglutination test was received, which was, it must be admitted, unexpected. The patient's serum was then sent a second time to the laboratory and was again found to agglutinate the *Bacillus typhosus* in the usual dilutions, while with paratyphosus beta there was only slight agglutination and with alpha none at all. Two urinary cultures were negative, but from a third culture a free growth of *Bacillus typhosus* was obtained. This also was confirmed by a fourth examination.

November 19. The patient was better and the temperature lower and the signs at the right base were less marked. The urine no longer showed the large cells seen the previous day, but instead a few clumps of polymorphonuclear leukocytes.

November 20. A fluoroscopic examination revealed no lung pathology and no evidence of subdiaphragmatic abscess. The temperature was normal all day; pulse and respiration about normal.

November 21. The patient was better and had less pain. Signs at the right base had wholly disappeared.

Phenolsulphonaphthalein elimination: 50 per cent. in two hours.

November 24. Patient much better. Temperature below 99°. Still complained of pain at night, which was now exclusively on the right side. Tenderness posteriorly was much diminished and there was none anteriorly.

Patient continued to improve and exhibited no new symptoms.

**Discussion.** There are many points in the report concerning which one would wish more information. It is, of course, impossible to be certain at what time the patient acquired the typhoid bacillus infection. It seems most probable that the febrile attack in July was true typhoid fever, since it was the only febrile illness in his

history, and since the possibility of catheter infection can be excluded also. Another important question which cannot be answered concerns the relationship between the symptoms of which the patient complained following the febrile attack in July and the occurrence of typhoid bacilli in his urine. If the patient was a urinary carrier it is difficult to explain the symptoms, for the carrier state is unfortunately peculiarly lacking in symptoms except in those carriers in whom there is sufficient gall-bladder trouble to attract attention. Whether "typhoid spine" may occur in carriers or bear any relation to the carrier state is unknown. Nor did this patient's symptoms agree entirely with the picture of "typhoid spine."

On the other hand the urinary findings in this case are not those of actual infection of the urinary tract with the typhoid bacillus. The typhoid bacillus may produce cystitis, pyelitis, pyonephrosis and even an acute urethritis, but in all these instances there is a pyuria in which the usual polymorphonuclear neutrophile predominates. No such pyuria was observed in this patient. A search of the literature reveals no statement as to the cellular elements in the urine of urinary typhoid carriers nor any description of the occurrence of phagocytic endothelial cells, although there seems no good reason why these cells should not reach the urine, as they are found in tubular nephritis lying free in the urinary tubules busily engulfing necrotic epithelial cells.

There is still doubt as to the origin of the typhoid bacilli found in urinary carriers, and the direct relation of gall-bladder infection needs further demonstration. The possibility of foci in the urinary bladder or even in the kidney has not been excluded nor has the possibility that under certain conditions, such as perhaps trauma or secondary infection, the quiescent foci of the carrier state might be transformed into active infection of the urinary tract. It is remotely possible that this case was an example of this kind.

Aside from these speculations, which are bound to be inconclusive, the fact remains that in this instance a most unusual cellular picture in the urine was observed, and, whether rightly or wrongly, a line of reasoning was followed which led to the discovery of typhoid bacilli in the patient's urine and of a positive Widal test in the blood serum.

This experience suggests that something may be learned from the study of the cells in the urine of urinary typhoid carriers, and that the recognition of endothelial leukocytes in the urine may be helpful diagnostically.

## A CONSIDERATION OF CERTAIN ASPECTS OF PROTEIN HYPERSENSITIVENESS IN CHILDREN.

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At the present time it is not unusual to see infants and children who are hypersensitive to proteins and who manifest their sensitiveness by a number of different clinical symptoms. Nearly everyone knows of individuals who are made ill, regularly, after eating fruit or shell-fish, or who are unable to come closely in contact with animals or grasses without developing hay fever or asthma. This idiosyncrasy or susceptibility to various substances has been recognized for a long time. Among the earlier medical writings on this subject are those of Elliotson,<sup>1</sup> Hutchinson<sup>2</sup> and Blackley.<sup>3</sup> Elliotson drew attention, in 1831, to the association between the pollen of plants and hay fever while Blackley, in 1873, not only recognized this association but produced edema and congestion of the conjunctiva by the instillation of certain pollens in the eyes of hay-fever patients. He also observed that the pollens produced an area of edema and erythema when rubbed into the abraded skin of such patients. In 1884 Hutchinson referred to a number of patients who complained of nausea, vomiting and abdominal discomfort, and he believed these symptoms were due to the eating of egg, as the symptoms disappeared when egg was withheld from the diet. He stated also that certain individuals might be susceptible to other articles of food, such as honey, tea, coffee and different fruits and vegetables.

The more common and characteristic features of hypersensitiveness to proteins, which occur in infants and children, are shown by the following case reports:

CASE I.—An infant, who had been exclusively breast-fed, was given, when six weeks old, a small amount of cows' milk. This was immediately vomited. One month later one-half teaspoonful of milk caused a severe general reaction. The baby vomited and had diarrhea. He became cyanosed and so prostrated that the physician considered him dangerously ill. Bread prepared with cows' milk brought on a similar reaction, as did the administration of three drops of a 1 in 12 dilution of condensed milk. Cows' milk in any form and in infinitesimal amounts always caused vomiting, loose stools, cyanosis, irregular respirations and prostration. He

<sup>1</sup> Clinical Lecture, March 31, 1831, *Lancet*, 1830-31, xx, 370.

<sup>2</sup> *The Pedigree of Disease*, p. 28.

<sup>3</sup> *Experimental Researches on the Cause and Nature of Hay Fever*, London, 1873: VOL. 160, NO. 3.—SEPTEMBER, 1920. 12

was able to take goats' milk without any symptoms. In order to determine that the symptoms were due to cows' milk the protein of cows' milk was applied to the skin. This was followed by an area of edema and erythema after four hours. When introduced in this manner cows' milk caused the same general symptoms as when taken by mouth. Protein from beef, egg, horse serum, barley, human milk and goats' milk caused no reaction when applied to the skin. The baby was nursed at the breast and given supplemental feedings of goat's milk until ten months old, after which minute amounts of cows' milk was given by mouth. Gradually the amount was increased until the hypersensitiveness to cows' milk was overcome. The paternal aunt had an idiosyncrasy to shellfish and the paternal grandfather and great-grandfather had asthma.

CASE II.—An infant, aged two years, was breast-fed for two months, after which he was given a formula of cows' milk. Cereals, broths and vegetables were added subsequently. Eczema appeared when he was one month old, and it had been persistent. When one year old he was given a soft-boiled egg. This was immediately vomited and he was sick for several hours. Six months later egg was given and he again vomited. The protein of egg, cows' milk, barley, horse serum and beef gave a marked reaction when applied to the skin. By omitting eggs, meats and milk from the diet the eczema improved, and by giving them in small amounts and gradually increasing them he was finally able to take these foods without a return of the eczema. The mother had eczema when she was an infant.

CASE III.—The patient, a girl, aged four and a half years, was breast-fed until she was ten months old. When eight months old an egg shampoo caused a severe urticaria of the head and face. About the same time the eating of a teaspoonful of custard caused a generalized urticaria, with marked swelling about the mouth. When twenty-two months old she became violently ill following the eating of custard, and was thought to have "ptomain poisoning." It was not realized at this time that the symptoms were caused by egg. Urticaria always followed the ingestion of egg in any form. Urticaria also followed the eating of peanuts and walnuts. The protein of egg was rubbed on the skin and a huge urticarial-like wheal appeared immediately. After forty-five minutes urticaria appeared all over the body and the eyes, ears, lips and vulva became swollen and red. The patient became nauseated and complained of abdominal pain and faintness. This patient has not been treated for hypersensitiveness to egg. A maternal aunt was sensitive to egg.

CASE IV.—The patient, aged four years, was given a small amount of egg when eight months old. She vomited immediately and had a generalized urticaria. Subsequently she was able to take egg in the small amount contained in cakes and pastry. When

eighteen months old asthma began. When the protein of egg was applied to the skin a huge urticarial-like wheal appeared. Egg and foodstuffs containing egg were excluded from the diet and she remained free from asthma for a year. Asthma then recurred. The protein of a number of different substances was applied to the skin and very definite positive reactions to cows' milk and beef were found. When egg, milk and meats were withheld the patient did not have asthma.

CASE V.—This patient was nine years old. When two years of age eczema appeared for the first time and persisted for four years. After that urticaria appeared and the eczema improved but did not entirely disappear. When eight years of age asthmatic attacks began and they recurred at rather frequent intervals afterward. It is interesting that the ingestion of cereals always caused a swelling of the mucous membranes of the mouth, which was accompanied by severe itching about the mouth. The protein of egg, beef, milk, oatmeal, barley and wheatena caused marked edema and erythema when applied to the skin. This patient is now undergoing treatment for hypersensitiveness to protein. A maternal aunt has asthma and the maternal grandmother has hay fever.

CASE VI.—The patient, aged ten years, was breast-fed four months and then weaned on account of a severe and extensive eczema. After the first year the eczema was less severe, but it persisted, and at the time of admission to the hospital, eczema involved the face, the flexor surfaces of the arms and the scrotum. Many different forms of treatment had been tried unsuccessfully. The sensitiveness to proteins was observed when six months old, when he was first given egg. Egg, fish and nuts always intensified the eczema, and the eating of any of them was followed almost immediately by a burning sensation in the throat, vomiting, diarrhea, edema of the lips and ears and urticaria. In addition to these manifestations, association with horses always causes urticaria and hay fever. A marked reaction of the skin was obtained with the protein of milk, egg, horse serum and horse dander. The patient was relieved by withholding egg, milk and meats from the diet, and, after being desensitized to them, has had no return of the symptoms.

Within the past few years much information relating to the nature of the symptoms, which are caused when a sensitive person comes in contact with various substances, has been obtained.<sup>4</sup> It has been established definitely that the symptoms in these cases

<sup>4</sup> The reader is referred to the articles by the following writers who have contributed largely to this subject and from which I have quoted freely: Schloss, O. M.: *Am. Jour. Dis. Children*, iii, 341. Talbot: *Boston Med. and Surg. Jour.*, 1914, xlxxi, 708. Longcope, W. T.: *Harvey Lecture*, 1915-16, p. 271. Cooke, Robert A., and Vander Veer, Albert: *Jour. Immun.*, i, 201. Walker, Chandler: *Oxford Medicine* ii, 115. Rackemann, F. M.: *Boston Med. and Surg. Jour.*, 178, 770. Kolmer *Infection, Immunity and Specific Therapy*, second edition, p. 614.

are due to protein which is contained in the substances to which the patients react.

In many ways human sensitization, as it is generally termed, is analogous to the anaphylactic reaction in animals. There is a close similarity between many of the clinical manifestations observed in man and those seen in anaphylactic shock in animals. The specific skin sensitiveness in animals and the skin reaction observed in serum disease closely resemble the protein skin reaction, which constitutes an important feature is the condition under discussion.

It is not necessary in this communication to give in detail the many experiments which have been undertaken to demonstrate a relationship between human sensitization and experimental anaphylaxis in animals. Human sensitization is not identical with the artificial sensitization with antitoxin sera or with experimental anaphylaxis in animals. They differ in certain respects, and definite conclusions should not be drawn until these differences have been subjected to more careful experimental investigation.

The hypersensitive state may be present at birth, and this is the rule in a large percentage of the cases, so that severe and even alarming manifestations result at the primary contact with the protein. In the case reported by Park,<sup>5</sup> vomiting and diarrhea and cyanosis and prostration were induced when the infant received for the first time only a small amount of cows' milk. Less severe manifestations, as eczema, urticaria and asthma, may develop as well when the protein is first given. The symptoms may not, however, be manifest at the initial contact with the protein but develop at a later period, as illustrated by the following case. Egg albumen was given to an infant of three months for several days without any apparent reaction. When a coddled egg was given at the age of nine months, however, vomiting, generalized urticaria and asthma followed immediately. In other cases evidences of protein sensitization may be present during infancy and then entirely disappear, but after several years either similar or, as more often is the experience, different clinical manifestations develop. Thus a patient who has never received egg or cows' milk may have eczema throughout infancy which entirely disappears, to be followed in early childhood by asthmatic attacks with or without eczema. It is easy to understand the constant production of symptoms in a person once he has become sensitized to protein, as the avenues for entrance of protein are so very numerous and the patient is so constantly brought in contact with protein; but the manner in which the primary sensitization takes place is not so readily explained.

Sensitization may be acquired, it may be conveyed from the mother to the infant or it may be inherited. It is quite conceiv-

<sup>5</sup> A Case of Hypersensitiveness to Cows' Milk, *Am. Jour. Dis. Children*, xix, p. 46.

able that a person might become sensitized through an open wound in the skin, through the mucous membranes of the gastro-intestinal tract and various other ways. Sensitization is acquired undoubtedly in one of these ways in a certain number of cases. The transference of sensitization from an animal to the offspring, which has been demonstrated by Wells<sup>6</sup> and others, would suggest that human sensitization might take place in the same way. While not improbable it undoubtedly is infrequent. Experimental transference of sensitization differs greatly from human sensitization. In animals the sensitization transferred from the mother lasts but a few weeks and is not transmitted from generation to generation, while in human sensitization quite the reverse obtains. In all probability sensitization is inherited in those patients who exhibit manifestations when they are brought in contact with the protein for the first time. A family history of sensitization can be obtained in nearly all of these cases, and there are numerous cases recorded in which the sensitization has been transmitted through several generations. The sensitization, which does not have to be to the same protein, may be transmitted through the maternal or paternal ancestors. The studies of Vander Veer and Cooke substantiate this view. They showed that hypersensitiveness to protein may be inherited, and that in a general way it follows the principles of the Mendelian law of heredity.

Hypersensitiveness to protein may be established by observing the clinical symptoms which are caused by the different substances and from the history. A history of hypersensitiveness may be obtained not only from the immediate members of the family, but in the family history dating back for several generations. The occurrence of asthma, eczema, urticaria, etc., in any member of the family is suggestive evidence of hypersensitiveness. Such a history is found in a large proportion of the patients, as illustrated by the following cases: A patient, aged five years, who suffered from asthma, gave a history of asthma having occurred in the paternal great-grandfather, grandfather and the father. The skin test in this patient was positive to the protein of egg. In another patient who had asthma following the ingestion of egg the first and second cousins had an idiosyncrasy to egg.

The symptoms oftentimes are so striking and so characteristic that they afford abundant proof of hypersensitiveness. In other cases the symptoms may be so indefinite that the illness does not appear to be related to protein sensitiveness. The local reaction which is produced when protein is applied or injected into the skin of hypersensitive persons is accepted by the majority of observers as an evidence of this state. The cutaneous or intracutaneous method may be employed for this purpose.

<sup>6</sup> Jour. Infect. Dis., 1911, 160.



In the cutaneous method the skin is scarified with a needle or von Pirquet scarifier and the substances used for the test gently rubbed in. The scarification should be superficial and blood should not be drawn. A positive reaction is shown by the appearance of an urticarial-like wheal at the point of scarification. The reaction appears within the first five minutes, increases rapidly and reaches its height in ten to fifteen minutes. It gradually subsides, but in the majority of instances the edema persists thirty minutes or more. A control test should always be made, as in certain individuals a slight erythema with edema may appear at the point of scarification alone. A slight reaction may take place about the substances which react negatively, but it is easily differentiated from the positive reactions. It is never so intense and disappears within ten to fifteen minutes. The pure dried proteins for this test may be obtained from a number of commercial laboratories. When they are used a drop of tenth normal sodium hydrate solution is mixed with the dried proteins to facilitate solution.

In the intracutaneous method the protein in solution is injected into the skin by means of a small tuberculin syringe and fine needle. A positive result is indicated by a reaction similar to that obtained with the cutaneous method. The erythema and the edema gradually increase and attain their maximum height in the first fifteen minutes. They persist usually for thirty minutes or more. A reaction often occurs at the site of the control and of the negatively reacting substance, but it is never so intense, and the area of edema reaches its maximum diameter in five to ten minutes and gradually subsides within fifteen to twenty minutes. At times the erythema marking the site of the injection may persist in positive reactions for from twelve to twenty-four hours. It is advisable to observe the reaction for some time, for that which may at first appear to be a negative reaction occasionally becomes a positive reaction (delayed). The true reaction has to be differentiated from the traumatic or non-specific reaction which sometimes occurs, but this should not be difficult. When the reactions are negative by the cutaneous method they should be repeated with the intracutaneous method. The reactions from the intracutaneous method are more difficult to interpret than are those from the cutaneous method; on the other hand, they are more delicate. As a rule the reactions are sharp and distinct and with experience a differentiation between negative and positive reactions is not difficult.

When properly performed and interpreted, accurate information regarding the sensitiveness to the proteins tested is obtained with this test. A positive reaction indicates sensitization and a negative reaction indicates non-sensitization. Equivocal reactions may occur. A patient may exhibit clinical manifestations and give a negative reaction or a positive skin reaction may be present without the patient giving any clinical signs of sensitiveness. These are

exceptions to the rule and are seen infrequently. Care should be used in making the tests, as severe and alarming symptoms may follow the application of protein to the skin in the highly sensitized patient. One infant, hypersensitive to cows' milk, had a severe systemic reaction following the cutaneous application of a dilute solution of cows' milk, and another infant with a generalized eczema presented the symptoms of anaphylactic shock following the intracutaneous injection of a 1 to 100 dilution of egg white. Also a boy of seven years, who was hypersensitive to egg, reacted violently with urticaria, angioneurotic edema and asthma after the cutaneous application of a 1 to 100 solution of egg white. Similar reactions have been observed in other patients. The most severe reactions have followed the test with the proteins of egg white, cows' milk and of pollens. That systemic reactions may follow the inoculation of protein in the skin of a sensitized person is not surprising when one considers the infinitesimal amount of protein which will incite an attack of asthma in a person sensitive to horse dander, the pollens of grass, etc. In infants and children the reaction to only one protein should be determined at a time and the cutaneous method should be tried before the intracutaneous method.

Infants and young children, as a rule, are not sensitive to such a variety of proteins as are adults, but even in them a number of different proteins have to be used in testing for sensitization. The protein of egg, milk, cereals and meats, horse serum and dander, timothy, red-top and rag-weed are the more common substances to which children are sensitive. The selection of the proper proteins for the test, obviously, is a matter of much practical importance. Information necessitating the test with other proteins may be obtained after careful investigation. This is illustrated by the unique experience with a young girl with asthma who gave negative reactions to the proteins used in the routine tests. The asthmatic attacks occurred only when the patient was in one locality. After careful questioning it was found that the attacks were incited by handling purple asters.

As mentioned above, attention is usually attracted to this condition by the occurrence of eczema, asthma, hay fever, urticaria and angioneurotic edema or from the history of vomiting and diarrhea and general prostration when a certain food is given. The symptoms may be limited to one manifestation or various manifestations may occur in the same patient. The degree of sensitization as determined by the symptoms varies not only in different patients but in the same patient from time to time. Patients are frequently seen who come in contact with the offending protein, and yet there may be no clinical manifestations or they may be slight for long periods at a time, and then a severe reaction will occur. On the other hand, even the most minute quantity of the offending protein

is followed regularly by a violent reaction. The patient may lose his sensitiveness altogether or it may persist through life. Sometimes sensitiveness to other proteins is acquired.

All investigators have observed in these patients that there may be not only the history of sensitiveness to a number of substances but that the skin test is usually positive to more than one protein. The same patient may be sensitive to any one protein or to any combination of proteins from the same animal, or from the seed, the pollen and the leaves of a plant. On the other hand the same person may be sensitive to a number of proteins less closely related, as the protein derived from a plant and from an animal. This is true in asthma and eczema, in fact, in all of the clinical manifestations of protein sensitization. In the patient studied by Schloss, positive skin reactions were obtained to egg, oatmeal and almonds. In the patients with eczema studied by the writer,<sup>7</sup> positive reactions were obtained with the protein of human milk, cows' milk, barley and horse serum. A patient of seven years with eczema, urticaria and hay fever gave positive reactions to the protein of egg, barley, horse serum, walnuts and rag-weed. That these patients are sensitive to more than one protein, even closely related proteins and to proteins unrelated biologically, is not so surprising when it is remembered that the specificity of the anaphylactic reaction in animals is determined not only by the biological origin of the proteins but by their chemical structure.

A phenomenon comparable to the refractory state or anti-anaphylactic state in animals is occasionally seen. Schloss<sup>8</sup> observed this in two patients who developed a generalized urticaria within one to three hours following the ingestion of egg. The positive skin reaction disappeared for twenty-two to forty days, and during this period the ingestion of egg was not followed by the usual clinical manifestations. With the reappearance of the skin reaction, egg again caused an urticaria. In one patient with asthma due to egg, whom I was desensitizing by subcutaneous injection of the protein of egg, a similar phenomenon occurred. A severe attack of asthma was precipitated by the ingestion of egg which the child obtained without the parents' knowledge. The skin reaction was positive for a period of ten days, after which the reaction was not determined, but the asthma did not recur for nearly two months; during this time she ate egg daily. It would be of much therapeutic value were it possible to produce the refractory state in a sensitized patient, but at present no satisfactory method has been devised.

Treatment of patients with hay fever and asthma due to the inhalation of pollens, the emanations from animals and absorption

<sup>7</sup> Blackfan, K. D.: *Am. Jour. Dis. Children*, xxi, 441.

<sup>8</sup> *Tr. Am. Pediat. Soc.*, 1915, xxvii, 60.

from bacterial proteins has been extensively carried out by a number of workers. The procedures employed are so well known that further reference will not be made to them here. I shall, however, mention briefly the essential principles regarding the management of those patients who, on account of their hypersensitiveness to the various foods, develop eczema, urticaria, asthma, etc.

The treatment may be carried out by absolutely omitting the protein from the diet or by the process of desensitization. In certain cases a combination of these methods may be used.

Omitting certain proteins from the diet may occasion so much difficulty that it is oftentimes unsatisfactory even with the undivided attention of a responsible attendant. Also such a procedure should be undertaken with caution, especially in infants, as much harm can be done if in addition to the symptoms of hypersensitiveness there are added severe disturbances of nutrition. This is particularly liable to occur when milk is withheld from the diet of infants with eczema. In these patients, although it has been shown that the eczema can be benefited by temporarily withholding milk and other protein foods, it seems to me that treatment of their hypersensitiveness should not be started until they have reached the age when milk does not play such an important role in their nutrition.

It may be found by experience that the absolute omission of the protein is not necessary, as there is a very considerable variation in the reaction of different patients to the ingestion of various food proteins. A patient may be able to eat small quantities of a food without symptoms while large amounts bring out a severe reaction, or a patient may be able to take the food if it has been subjected to a high temperature, which renders the active properties of certain proteins inactive. The specific protein may not be present in a sufficiently high percentage in certain foods to bring about a reaction when ingested even though a positive skin test has been obtained.

Desensitization of the patient to protein is by all means the most satisfactory method of procedure. The time required for desensitization depends largely on the degree of sensitiveness and varies with each patient. The subcutaneous injection method is tedious, and, as it is particularly trying to infants and young children, I have come to rely almost entirely on desensitizing them by administering the protein by mouth. Meats, milk and cereals may be given in small amounts in solution. The protein of egg is best given in capsules.<sup>9</sup> The initial dose is that which fails to give a

<sup>9</sup> I am indebted to Mr. Dunning, of Hynson, Westcott & Dunning, of Baltimore, for his assistance in the preparation of the egg-white in capsule form, which has been used in these cases.

positive skin reaction. The rapidity with which the amount is increased depends to a great extent on the degree of sensitiveness. In each case the process of desensitization should be controlled by frequent skin tests. The aim should be not only to have the patient able to ingest the protein without a systemic reaction but to secure a negative skin reaction. It is surprising how difficult it may be to accomplish the latter. For practical purposes desensitization may be said to be completed when the patient is taking average amounts of the substance without recurrence of the symptoms. It should be remembered that the proteins, even after the patient has become able to take them by mouth in quantity, must be given regularly, as there is always the possibility of a return of the symptoms if this is not done.

Patients with only one clinical manifestation, as those who suffer from eczema, urticaria or asthma, and in whom there is a positive skin reaction to only one protein, should be given a diet from which the protein has been excluded. This should be maintained until the symptoms have disappeared. After that, desensitization may be begun by the administration of the protein to which he is sensitive.

Patients who are susceptible to a combination of proteins are the most difficult to treat. The special proteins to which they are sensitive should be excluded from the diet, and in addition protein from eggs, meat and milk even if a negative skin test is obtained to them. The reason for excluding such foods is more or less empirical. After the clinical manifestations have subsided entirely the proteins to which the patient is least sensitive, as shown by the skin test or by the reaction following their ingestion, are administered. After there has been no return of the symptoms for some time the process of desensitization with the protein which gives the most intense reaction may then be commenced. Recurrence of the symptoms at any time necessitates the withholding of the special proteins from the diet until the symptoms have subsided. Desensitization is then begun again.

Successful therapeutic results may be expected in patients who are unable to take various foods without the development of eczema, urticaria, asthma, etc., if the patients are hypersensitive to protein and if the treatment is consistently and thoroughly carried out.

## THE COLON IN CONNECTION WITH CHRONIC ARTHRITIS (ARTHRITIS DEFORMANS).<sup>1</sup>

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In July, 1912, a single woman, aged thirty-four years, a school-teacher, was referred to me for treatment of an intestinal condition. She had a typical polyarthritis involving the phalanges, wrist, elbow, tarsal, ankle- and knee-joints, which in five years had reduced her to an invalid's chair existence. Her relapses of joint involvement were frequent, each attack rendering the joints more crippled in a permanent way. A constipation came on with the initial joints affected (both elbows), and she stated that if her bowels had not moved that day she was distinctly stiffer throughout the body that night. She had lost weight, her tissues were flabby, a psoriasis had developed, the liver was noticeably enlarged and there was a slight amount of albumin in the urine, with many granular casts. The studies of the feces showed the presence of gas-bacillus infection of the gut. She was treated by a diet high in calories, but low in calcium, and by strains of viable *Bacillus coli* rectally administered. The treatment was kept up for seven months, at which time she was markedly improved. In the fall of 1913 she resumed her work as teacher of French in the Wadleigh High School and has not lost a day since. She lives the life of a normal woman, attends to her apartment after school hours, cooks her own foods, goes to the theater and dances in the evenings, and, with the exception of some crippled joints, in which there has not been one remission from the beginning of treatment, she is a normal woman.

This happy result in the treatment of an intestinal toxemia seemed to qualify me in the eyes of some lay people as one especially able to treat such conditions. In the New England town that the case came from there were three others that soon were under observation, and from this nucleus it has spread from Maine to Pennsylvania until today 79 cases, supposedly like hers, have been seen. These have comprised a group of cases that deserve recording, both as to the findings and results accomplished. Of these, 31 were deemed unsuitable to be classed as typical ones of polyarthritis. They were made up of instances of gouty joints, syphilis, myositis, true articular rheumatism more or less resolved, acute joint involvement from manifest focal infections that were easily removed (nothing more being done in the treatment of the arthritis), and 3 extreme cripples so seriously involved with manifest disease of internal organs (mainly

<sup>1</sup> Read before the Academy of Medicine, March 19, 1920.

liver, kidneys and heart) that they were judged unfit for both study and treatment. The 45 remaining ones I desire to present.

Of these the average duration of joint involvement was three and seven months. The knee-joints, left, right or both, were initial in 12 cases, the ankles in 7, the elbows in 11 and other joints in the 7 remaining. Manifest focal infections were present in the tonsils in 13; in dead tooth pulps, apex abscesses and pyorrhea, in 10; urinary tract, 3; appendix, 3; gall-bladder, 2; prostate gland, 2; female pelvis, 1; head sinus, 1. This makes 35 of 45 having manifest infection. An infectious disease of years before, healed or dormant tuberculosis, cystitis without involvement of the pelvis of the kidney or substance, boils, etc., were thrown out of etiologic consideration; 14 were men and 31 were women. The average age of the 45 cases was thirty-one years when seen by me.

The 13 tonsil cases were properly operated upon, 1 requiring a second operation for a tab of tonsil tissue that was left behind the left anterior pillar. Improvement in the joints was quickly noticeable in 4, believed to have come about by the patient in 3 more and none being noticeable in 8. The one that showed the most marked benefit in the joints got the worst relapse. She had this six months after operation and then came under observation and study. The second best case had a relapse in the fifth week after enucleation. They were all advised to remain away for three months after operation unless the joints became noticeably more involved. In the course of seven months they all had come back with added frank joint involvements.

In the 10 oral sepsis cases the best possible attention was given. Extraction of teeth was the rule, this being done uniformly throughout the group. The devitalized teeth with apex abscesses were opened through the apex ostium and drained for three weeks. Each tooth canal was filled with gutta-percha through the apex opening; until that was accomplished it was not considered sterile. With the amputation of root ends and surgical attention to pyorrhea, as well as insistence on mouth hygiene as a daily practice, the cases were handled according to the best of modern dental attention. In some of the cases (six in number) the work extended over months of time. Thus definite time allowance for return of joint relapses was not practical. One of the cases, one of general pyorrhea with apex abscesses and extraction of all of the teeth, claimed marked benefit in the joint symptoms with but one slight relapse in three years. The patient feels the benefit satisfactory enough not to warrant a long trip to New York City for further study and observation. The other 9 cases came under observation even after all of this work, expense, pain and trouble. On the occasion of relapse, or there being no benefit in the joint symptoms, films were again taken of the teeth so that this source of infection could definitely be thrown out of consideration. In the six that had relapses the average

length of time of this after the dental work was concluded was seven months. The other three had no joint benefit whatever.

The 3 appendix cases were operated upon, 1 claiming a moderate benefit, but relapses establishing themselves in the second month afterward. The 2 gall-bladder cases (both cholelithiasis with chronic cholecystitis), in which cholecystectomy was done, were not improved, one apparently being made worse by operation for unknown reasons. The 3 renal cases are difficult to conclude on. One was a woman with a badly diseased but 50 per cent. functioning left kidney. A Gram-positive bacteria was always present in the urine from that side. This organism was not identifiable but easily grown on blood agar, and a vaccine was made and administered subcutaneously. This was kept up for five months together with regular washing of the pelvis of the kidney on that side. A nephrectomy was then done, although the woman seemed to have been benefited in the joint symptoms. A generally diseased and vacuolated tuberculous kidney was removed. The urine cleared of pus and the vaccine organisms. On the tenth week after the operation, when distinct benefit was apparently coming about, a relapse in the joint symptoms occurred, rendering the patient unable to leave the bed for nearly three months. She was then moved to the city for further observation. The other 2 cases were those of *Bacillus coli* pyelitis that cleared on vaccine, hexamethylenamin, renal pelvis irrigations and length of time. No benefit occurred in either one in the joint condition even after the urine had been clear for three months. The prostate cases were enlarged prostates. Both were considered chronic disease of the seminal vesicles originally from Neisserian infection. Both were treated by massage, irrigations of and installations into the posterior urthra. One developed a prostate abscess when under treatment, was operated on and made a clear local recovery. Neither was benefited in the joint symptoms. A case of double pyosalpinx had both tubes removed with benefit only to the pelvic distress, and one of double ethmoidal disease with an infected superior maxillary sinus was thoroughly operated upon, drained and irrigated, also without other than benefit to local symptoms.

Here then were 35 cases of typical polyarthritis of the chronic type with focal infection, all of which were carefully and thoroughly treated in ways that are known to be the best, and yet all but one has received no benefit in the joint conditions. The 34 cases were finally placed under observation for metabolic and gastro-intestinal study, which with the 10 that showed no manifest focal infections made up 44 cases. Each was placed upon the following test diet, which was graded in instances of lighter weight than 140 pounds, according to what that would be:

"The diet mentioned is to be adhered to strictly for three full days, namely, seventy-two hours. The stools and urine of the first



forty-eight hours after its institution are of no value for examination. If constipation exists the bowels are to be moved by injection. After the forty-eighth hour from the beginning, providing the bowels have moved during that time, the entire next stool is to be saved and examined. No purges are to be taken, but a glycerin suppository or an enema may be employed to obtain the stool required. A covered small tin can or a glass jar can be used as a container. A twenty-four-hour collection of urine should accompany the stool, this being started at the end of the forty-eighth hour after the institution of the diet. Start with an empty bladder and void for the last portion at the twenty-fourth hour. Take no medication by mouth during the three days and continue your activities as you have been doing.

Morning: Two thin slices of well-baked bread, with butter liberally applied; one pint of oatmeal gruel, made of about 40 grams or  $1\frac{1}{2}$  ounce of oatmeal; 10 grams or  $\frac{1}{3}$  ounce of butter; 200 grams or  $6\frac{2}{3}$  ounces of milk; 300 grams or 10 ounces of water (all strained). One egg cooked in any form.

11 A.M.: Milk, one-half pint or one glassful.

Noon: A good-sized piece of steak or roast beef, chopped or cut into very fine pieces, about 200 grams or 4 ounces, and served on a slice of toast; one bowl, about 250 grams or  $8\frac{1}{3}$  ounces, of mashed potato, with 20 grams or  $\frac{2}{3}$  ounce of butter.

4 P.M.: Milk, one-half pint or one glassful.

Night: Same diet as breakfast.

Water may be taken as desired.

Attention must be paid that this diet is followed precisely. The reason for this is that careful and extensive quantitative examinations are made of the specimens sent, and unless the rules are followed accurately the laboratory findings may be misleading."

During the last twenty-four hours (from the forty-eighth to the seventy-second hour) 40 c.c. of blood was extracted, ten being employed for the Wassermann test, the remaining 30 c.c. being placed in a bottle containing a few drops of 20 per cent. potassium oxalate solution. The blood was taken at about the forty-eighth hour from the onset of the diet before breakfast.

The Wassermann test was negative in all of the instances. This is not surprising, because of all of the cases in which a positive Wassermann was present, mercurial injections were carried out as a routine. Nine of the focal infection cases had a positive Wassermann, all receiving mercurial injections during the time they were under observation by others, and those that gave a definitely positive Wassermann at the initial examination were judged syphilitic and are not included in the 45 cases reported. Still it was considered wise to do another Wassermann before the beginning of the metabolic and gastro-intestinal studies. A case might have been missed in the first instance and be caught here, or a case might have begot a syphilis in the length of time of their operative

procedures. It was also deemed wise not to employ the ingestion of glucose before the blood was drawn. The reason of this is that because many instances of chronic intestinal toxemia show a sugar intolerance to this method. The sugar intolerance after ingestion of glucose is a finding in at least 20 per cent. of the saccharobutyric toxemias. Thus it was thought best to estimate the sugar content under normal conditions.

None of the 31 cases showed a hyperglycemia, taking 0.1 per cent. as the standard. In one of them a colorimetric reading of 35 (0.13 per cent.) was obtained, but subsequent examination did not sustain it.

The creatinin estimations averaged in 43 instances 2.2401 mgm. Taking 2.2375 mgm. as a standard, 13 of 31 cases were somewhat elevated. There were others, however, that were distinctly below this figure. Because in saccharobutyric toxemias about one-half of the cases show a slightly elevated creatinin content in the blood, these findings were taken as non-significant in so far as chronic arthritis was concerned.

The uric acid estimation in 29 cases gave an average of approximately 250 mgm. per 100 c.c. of blood. The same negative findings may be said of the non-protein nitrogen estimations, the average in 31 cases being 7.7. mgm. in 100 c.c. of blood. Cholesterol total solids and chlorides were not estimated. Several of the cases in which markedly reduced states of body existed showed slight degrees of acidosis. These findings were considered as a secondary condition and etiologically or symptomatically non-important. Many had degrees of simple anemia, sometimes with a lowering of the erythrocyte count.

In all of the cases routine examinations of the urine were made. Attention was paid to the indican and uroresine presence, and sulphate partitions were made in all of them. The presence of an excess of the conjugate sulphate, oxalic and uric acids and a chloride and total solid decrease were considered significant. Forty-four urines with abnormal findings were found.

The stools were carefully examined; notes were made of reactions; study of food detritus; search for ova (none found); estimation of mucous content; Gram-differential studies and relative countings; the fermentation tests and studies of gas contents and character; studies of sedimentary bacterial growths grown anaërobically and aërobically, with animal inoculation, were done. Taking normal standards there were forty-four departures from it. Thus with the urine and stool findings there were 44 instances of chronic intestinal toxemias: 34 were saccharobutyric in type, 2 were indolic and 8 were of mixed form.

From this practically complete significance of the colon as a cause of arthritic symptoms the cases were treated by diet, suitable to the type of toxemia and vaccines, all of the cases being kept under

treatment at least five months and diet alone advised for a year afterward. The plan of vaccine treatments and the diets employed were according to the author's methods,<sup>2</sup> in which the biochemical alteration method was not found necessary in any of them.

#### BACTERIAL TREATMENTS IN PRIMARY TOXEMIAS (RECTAL AND SUBCUTANEOUS METHODS AND VACCINE IMMUNITY).

Saccharobutyric	{	B. <i>aërogenes</i> capsulatus (rectal).
		Gram-positive diplococci (skin, rarely; rectal, rarely).
		Gram-positive single cocci (rectal).
		B. <i>bifidus</i> (rectal rarely).
Indolic	{	B. <i>putrificus</i> (rectal rarely).
		B. <i>coli</i> communis (rectal, skin).
		B. <i>mesentericus</i> (rectal).
		B. <i>liquefaciens</i> (rectal).
		B. <i>proteus</i> .
Mixed	{	Gram-negative streptococci (skin).
		Staphylococci (skin).
		Combination of above according to predominance of fermentation or putrefaction and types of organism.
Mixed	{	The rectal method is used here altogether, and effort is made to get reactions and a leukocytosis of from 10,000 to 20,000 within eight hours after the injections.

#### BACTERIAL TREATMENTS IN PRIMARY TOXEMIAS (RECTAL AND SUBCUTANEOUS METHODS AND BACTERIAL ANTAGONISMS).

Saccharobutyric (heavy protein diet)	{ <ul style="list-style-type: none"> <li>B. <i>aërogenes</i> capsulatus</li> <li>Gram-positive diplococci</li> <li>Gram-positive single cocci</li> <li>B. <i>bifidus</i></li> </ul>	{ <ul style="list-style-type: none"> <li>B. <i>coli</i> (many different strains and perhaps collected from different sources); for the first two <i>a</i> and for the second two the <i>b</i> strains are best.</li> </ul>
Indolic (low protein and high carbohydrate and hydrocarbon diet)	{ <ul style="list-style-type: none"> <li>B. <i>coli</i></li> <li>B. <i>mesentericus</i></li> <li>Gram-negative streptococci</li> <li>Gram-negative staphylococci</li> <li>B. <i>proteus vulgaris</i> (B. Welch)</li> <li>B. <i>cloaca</i> (B. <i>coli</i>, polyvalent strains)</li> <li>B. <i>pyocyaneus</i> (B. <i>coli</i>, <i>a</i> strains)</li> <li>B. <i>putrificus</i> (B. <i>coli</i>, <i>b</i> strains)</li> </ul>	{ <ul style="list-style-type: none"> <li>B. <i>acidophilus</i></li> <li>B. <i>bulgaricus</i>.</li> <li>B. <i>lactic aërogenes</i>.</li> </ul>
Mixed (least possible amounts of food, no cheese; peeling of fruits; mostly boiled foods)	{ <ul style="list-style-type: none"> <li>No action on antagonisms possible by rectal or subcutaneous methods excepting when a predominant type of bacteria is present.</li> </ul>	

The difference between the *a* and *b* strains of *Bacillus coli* is that it does not produce gas in saccharose; the *b* does. The effects are the same on all the other sugars and on the coagulation of milk.

Occasional recourse in the debilitated cases to the low calcium diet as advised by Bovaird was employed. This, however, was not considered specific in any sense, but is useful in building up general tone and vital strength. Anticonstipation additions of bran preparations, prunes cooked in lactose sugar, fruits twice a day, water in abundance, agar-agar, etc., were often required. A weekly dose of castor oil was advised. No physical measures of treatment were allowed until the relapses had ceased and the case had made marked improvement. Experience proved that while an occasional case is benefited by physical treatments the majority are not when relapses were running or liable to occur. The best time to begin physical treatments is from six months to one year after the last relapse, the later the better the results from them.

Cure cannot be figured in this disorder. One cannot by any treatment restore diseased tissue. Joints which have atrophy of cartilage, absorption of bone, hyperosseous growths, ankylosis, etc., never could return to normal even were one to employ a specific treatment on the cause. The mischief is done when the deformity is present. Benefit could be judged by stopping of the relapses, reduction of swelling and pain of the joints and general improvement of the body and increase in usefulness of the joints. In addition, all of these would have to be viewed with a conservative attitude. In a group of cases one sees not uncommonly some that for some unknown reason have run a short course of slight involvements and then no more progression. The next case in the same several months of time might be bedridden with ebonization of all of the joints. In groups the cases run very irregularly. With the majority, however, the tendency is downward by relapse, the already affected joints becoming worse and the non-involved joints becoming affected. The only standard to figure benefit on is a relative one based on how the patient was before treatment and how afterward in sustained ways. The cessation of relapses is an important factor in this, in my opinion the most important one. Reduction of swellings of the joints is accomplished only in the periarticular tissues, and it is by these two that increased usefulness of joints is accomplished. What, perhaps, is the next important factor in some of the cases is an improvement in general body, such as in the loss of weight, condition of body tone, the anemia, a secondary renal disturbance that may and often does approximate a true nephritis and status of tone and function of the liver and heart. Thus in any case we can only record improvements and perhaps classify them as none, moderate or marked.

In 44 cases treated by the measures mentioned, marked improvement was observed in 21, moderate in 19 and none at all in 4. Those that had physical measures of treatment, late after the diet and vaccine treatments, made more marked benefit in all but 9, this including the 4 mentioned above.

**Conclusion.** Focal infections are commonly met with in cases of arthritis deformans, which, when corrected surgically, do not actually benefit the chronic cases, although it may be striking in results in arthritis of only a few weeks' or months' standing.

The tonsils are the most often affected, the teeth next and other sites less frequently. The colon, however, was the commonest source of infection of them all, the organisms met with in order of frequency being the *Bacillus aërogenes capsulatus*, diplo- and single Gram-positive cocci, *Bacillus putrificus*, pathogenic types of *Bacillus coli communis*, staphylococci and streptococci.

On the basis of what can be estimated by blood chemistry today there is no reason to believe that arthritis deformans is due to constitutional errors, a view commonly held, particularly by the older clinicians. It is far more logical to believe that the condition in each instance is due to focal infection somewhere in the body, the intestinal canal being the most frequent site.

Whatever manifest focal infection is found should be treated surgically, and when no benefit is noted, complete examination of stools and urine are in order because treatment directed here is well worth the trouble in the results probable of being accomplished.

Dieting according to the type of bacterial infection (toxemia) present in the gut and bacterial treatment commonly offers distinct benefit in the cases.

Constipation and debility should be corrected by diet and not by drugs.

There is no possibility of cure in the true sense, only benefit can be accomplished, and when this is sustained over lengths of time it represents the best that can be accomplished. Joints crippled by changes in the anatomy remain that way permanently.

There is good reason to believe that in the early course of this disorder if attention is given to the colon as well as to the other focal infections many would be saved a fate of chronic joint deformity and invalidism.

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### IMPROVEMENT IN GRAVES'S DISEASE SUBSEQUENT TO SEVERE FOCAL INFECTION.<sup>1</sup>

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(From the Department of Internal Medicine, University of Michigan Medical School.)

WE have recently had occasion to study two patients with Graves's disease, both of whom manifested very great improvement subsequent to severe acute infection.

<sup>1</sup> I wish to express my thanks to Dr. Newburgh for the privilege of reporting these cases.

As is well known, many writers have repeatedly pointed out that infections of any sort may have a markedly deleterious effect upon the thyroid, and, indeed, infection has been given an important role in the etiology of Graves's disease.

Vincent,<sup>2</sup> for example, has reported that of 156 cases of acute rheumatic fever which came under his observation, 86, or 68.3 per cent., showed painful tumefaction of the thyroid gland which disappeared with the symptoms of rheumatism.

Billings<sup>3</sup> likewise has observed many instances of thyroid enlargement, usually of the chronic type, in which various focal infections were associated with evidence of thyroid intoxication.

Jennings<sup>4</sup> has reported two cases of measles occurring in patients with preëxisting Graves's disease. In one patient, in whom hyperthyroidism was marked, death resulted during the course of the measles. In the other hyperthyroid symptoms were mild, but the attack of measles so aggravated the condition of the thyroid gland that four weeks later surgical intervention was deemed necessary.

In those cases of Graves's disease which have come under our observation the appearance of an acute infection very commonly has led during the course of the infection to an exacerbation of all symptoms of thyroid disease. Accordingly the search for and elimination of focal infection has become an accepted routine in the medical treatment of this condition, and the improvement seen following the removal of such foci has frequently been striking.

With these facts in mind the occurrence of improvement as a result of infection seems at first thought to be paradoxical. However, as Beck<sup>5</sup> pointed out, one would expect the first effect of infection to be irritative, and hence productive of thyroid hyperfunction, and that later effects of the same infection may be degenerative changes leading to hypofunction. Indeed, Vincent<sup>6</sup> mentions one case in his series which would definitely fall in this category. Thyroid hypertrophy which had appeared in association with rheumatic fever gradually receded, so that at the end the gland was left sclerosed and atrophic. Several instances are cited by Beck<sup>7</sup> in which well-marked symptoms of thyroid insufficiency appeared following protracted acute infections. Hertoghe<sup>8</sup> feels that all infectious diseases of childhood and of later life fall heavily on the vitality of the thyroid gland. Similarly, Ord<sup>9</sup> states that often the

<sup>2</sup> Sur la Réaction Thyroïdienne dans le Rhumatisme Aigu et sur l'Origine Rhumatismale de certains Cas de Goitre Exophtalmique, *Compt. rend. Soc. de Biol.*, 1907, lxiii, 389.

<sup>3</sup> Focal Infection, *The Lane Medical Lectures*, 1917, Appleton & Co., p. 103.

<sup>4</sup> Two Cases Showing the Effect of the Incidence of English Measles upon Preëxisting Graves's Disease, *Lancet*, 1918, i, 906.

<sup>5</sup> The Relation of Chronic Infection to Thyroid Deficiency, *Southern Med. Jour.*, 1918, xi, 492.

<sup>6</sup> *Loc. cit.*

<sup>7</sup> Thyroid Deficiency, *Med. Rec.*, 1914, lxxxvi, 489.

<sup>8</sup> Myxedema, *Tr. Clin. Soc.*, 1888, xxi, 298.

<sup>9</sup> *Loc. cit.*

atrophy which results in myxedema is due to inflammatory destruction of the glandular tissue. Cases have been reported by Albo<sup>10</sup> and others in which influenza apparently precipitated symptoms of thyroid deficiency.

Whether or not the thyroid itself is actually invaded during infection can only be conjectured. That such invasion does take place is certainly not unlikely. McCallum<sup>11</sup> has suggested that infection reaches the thyroid from the pharynx and sets up in the gland a non-suppurative thyroiditis which destroys many of the cells and leaves scars through the gland, after which hypertrophy of the remaining tissue occurs. Gilbride<sup>12</sup> studied bacteriologically 14 operated cases of goiter, 6 of which were exophthalmic and 8 cystic in type. He succeeded in isolating *Micrococcus tetragenous* from one gland from the exophthalmic group, and from one gland from the cystic group he isolated *Streptococcus vermiformis* of Sternberg. Such study fails, however, to accurately represent the possible frequency of thyroid invasion. Operations are avoided during acute infection, and obviously it is during the period of active infection that we would expect the highest percentage of positive tissue cultures. It would be unwise to attach too much significance to the finding of *Streptococcus vermiformis* in the culture from one cystic gland, for the frequency with which this organism occurs as a contamination in tissue culture is well known.

We wish to present two cases of hyperthyroidism, both of which showed striking improvement following severe infection.

CASE I.—Mrs. C., aged forty-eight years, housewife, married, entered the hospital March 10, 1917, complaining of tumor in the thyroid region, palpitation of the heart and pain over the region of the ensiform. The family history was negative. She had never been pregnant, and until two years ago her menstruation was normal. At this time the flow became profuse and currettage was done. Save scarlet fever at twenty-two the past history was unimportant.

In the summer of 1916 she became very nervous and noticed a marked tremor of the hands which, during August, was so pronounced that she could scarcely handle dishes. She began to have drenching night-sweats, which persisted through the fall of 1916. On October 14 she became prostrated and would have fallen if someone had not supported her. She first noticed at this time a small enlargement in the thyroid region which had progressively increased in size until the time of her admission. She went to bed October 14 and remained there six weeks. For several weeks after getting up

<sup>10</sup> Postinfluenzal Thyroid Insufficiency, *Progresos de la Clinica*, 1919, vii, 122; *Abst., Jour. Am. Med. Assn.*, lxxiii, 157.

<sup>11</sup> The Pathology of Exophthalmic Goiter, *Jour. Am. Med. Assn.*, 1907, xlix, 1158.

<sup>12</sup> Culture from the Thyroid Gland in Goiter, a Bacteriological Study, *Jour. Am. Med. Assn.*, 1911, lvii, 1988.

she had attacks of pain under the sternum so severe that at times it was necessary to lie down. Tiredness, trembling and dyspnea

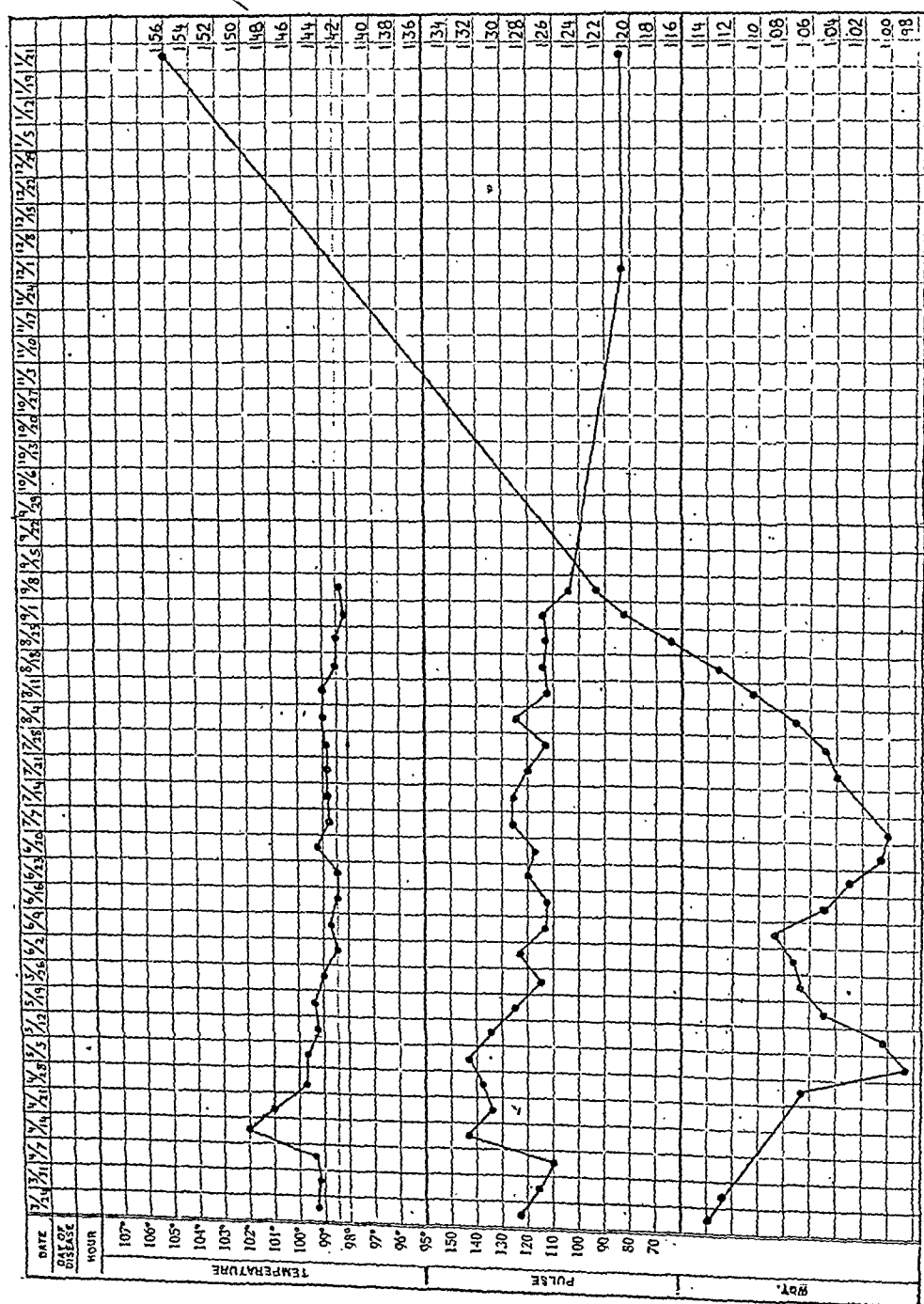


CHART I.—Case I. Chart showing temperature, pulse and weight by weeks. Average temperature and pulse readings for the period indicated are recorded.

were marked. There was no diarrhea and her appetite was quite variable. She had lost fifty pounds in the past year.



Examination March 13, 1917, showed a poorly nourished woman weighing 115 pounds. The skin was rather deeply pigmented throughout. Pupils were round, equal, rather widely dilated, but reacted normally. The palpebral fissures were widened and there was considerable lagophthalmos, together with failure of convergence. The forehead wrinkled normally on looking up. Scleræ and conjunctivæ were normal. The tongue protruded in the mid-line with marked tremor. Tonsils were slightly enlarged. There was slight bilateral enlargement of the thyroid gland. No thrill was noted, but a distinct bruit could be heard over both lobes. There was marked pulsation of the great vessels of the neck. Examination of the lungs revealed no abnormalities. The apex impulse of the heart was best felt in the fifth intercostal space in the mid-clavicular line. There was no enlargement to the right. The heart-rate was rapid and the sounds clear and forceful. No murmurs were heard. A-2 was greater than P-2. The abdomen showed nothing unusual. Except for a fine tremor on extending the fingers the extremities were negative.

The urine was negative. Blood-pressure, 155 to 85. Blood: red blood cells, 4,250,000; hemoglobin, 80 per cent.; white blood cells, 6800; differential count: neutrophile polynuclears, 69 per cent.; eosinophile polynuclears, 2 per cent.; small lymphocytes, 18 per cent.; large lymphocytes, 5 per cent.; transitionals, 3 per cent.; large mononuclears, 3 per cent.

She was placed in isolation, strictly confined to bed and given forced diet. By March 28 there had been no increase in her weight. On April 7 she complained of chilly sensations and her temperature was 101°. A few spots were seen in the posttonsillar region. There was some difficulty in swallowing solid food and she was placed on a liquid diet. Her white count at this time was 11,150. Throat culture was reported negative for Klebs-Loeffler bacillus. She grew rapidly worse, the tremor became very marked and she was excessively emotional there being some delusions. On April 15 respiration was of Cheyne-Stokes type, and there was considerable acetone in the urine. She was given sodium bicarbonate intravenously, and one hour following she had a chill lasting ten minutes. Throughout April 16 she was stuporous, but was easily aroused. She was slightly disoriented and there were involuntary bowel movements and incontinence of urine. The pulse was quite irregular, and she continued irrational on the 17th and 18th. By April 21 the tonsillitis had subsided. Blood culture taken April 13 was reported sterile on the 25th.

On April 28 the goiter had become smaller in size and had lost its hard feeling. Exophthalmos was somewhat less and lagophthalmos was absent. Nervousness was much diminished and she herself was conscious of improvement. During the week ending May 21 she gained five pounds, palpitation was less marked and the thyroid

gland was no longer palpable. She improved steadily until June 21, from which time her appetite became poorer and her weight, which had reached 108 pounds, had fallen by July 7 to 100 pounds, and she was quite depressed because of the apparent lack of progress. In the following week she began to improve again. July 14 she weighed 102 pounds; July 21 her weight was 104 pounds and on the 24th she was allowed to be up in a chair for the first time. She continued to gain weight, weighing 105½ pounds July 28, 107¼ August 4, 110 August 11, 113 August 18, 117½ August 26 and 120 September 1. At this time she felt fine and walked about the ward considerably. There had been but little diminution in the pulse-rate, but she no longer was conscious of palpitation. September 28 she weighed 122½ pounds and was discharged, feeling quite well. December 2, 1917, a letter from her stated that she was feeling perfectly well and her pulse averaged 85. On January 21, 1918, she returned for reexamination. She said that since leaving the hospital she had felt fine and she herself was convinced that no signs of the disease remained. Her weight was 156 pounds and examination showed her neck and eyes to be perfectly normal.

CASE II.—C. O., aged twenty-three years, male, machinist, unmarried, entered the hospital October 9, 1919, complaining of nervousness, weakness, tachycardia, exophthalmos and tumor of the neck.

The family history was negative. At the age of thirteen he had a perforating injury of the right eye. From the age of ten to sixteen there was almost a constant succession of boils, which he stated were cured by vaccine.

In April, 1918, he had a severe sore-throat, lasting two weeks, which was accompanied by irregular chills and fever, but without joint symptoms. On May 6, while operating an electrical machine he received a severe shock, which threw him to the floor and caused him to lose consciousness for a period of five minutes. After a short rest he was able, however, to go on with his work. That night at the supper table he noticed a tremor of the hands so marked that he was unable to hold a glass of water steadily. For the next two weeks he continued to work, but there was a gradual increase of weakness and loss of strength, so that at the end of that time he was hardly able to climb a flight of stairs, and he had lost fifteen pounds in weight. Early in June he was called by his local draft board and rejected for army service because of "leakage of the heart." This worried him considerably, and upon the advice of his physician he remained in bed for a period of three months, but made little improvement. His weakness and nervousness increased, his eyes became more prominent and he steadily lost weight in spite of an exceptional appetite. He entered the hospital October 9, 1919.

Examination showed a fairly well-nourished young man weighing 115½ pounds. There was marked exophthalmos, definite lagoph-

thalmos and failure of convergence. The right pupil was pyriform in outline, but both reacted to light and accommodation. Tonsils were moderately enlarged and the postcervical glands were palpable. There was a uniform soft enlargement of both lobes of the thyroid, and over both lobes a thrill was felt and a two-way bruit heard on auscultation.

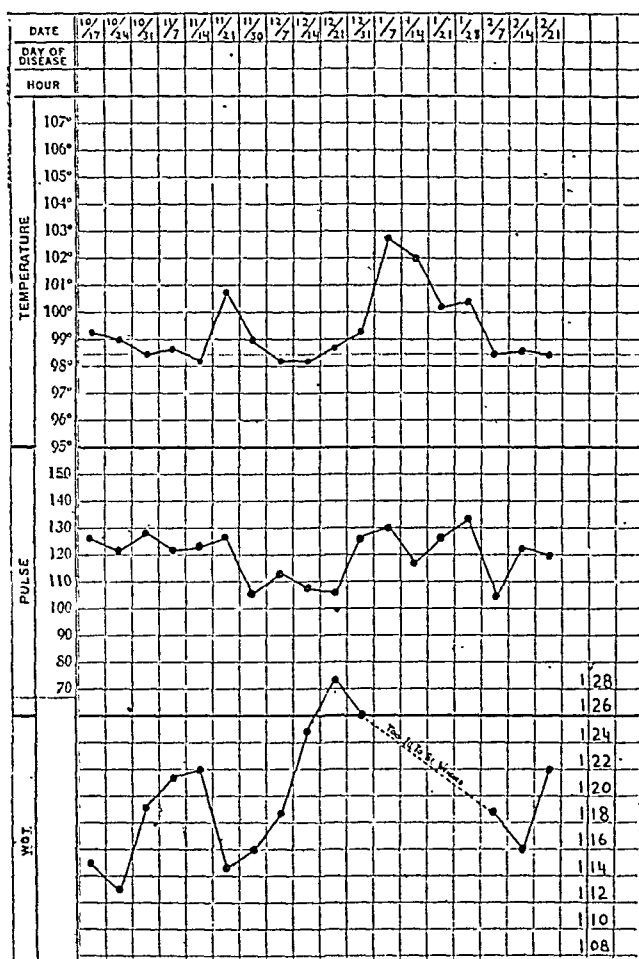


CHART II.—Case II. Chart showing temperature, pulse and weight by weeks. Average temperature and pulse readings for the period indicated are recorded.

The heart apex was in the fifth intercostal space inside the nipple line. The rate was rapid and regular, and a soft systolic murmur was heard best at the apex and was audible over the entire precordium, but was not transmitted to the axilla. A-2 and P-2 were about equal.

Chest and abdominal examinations were negative, and except for the typical fine tremor on extension of the fingers the extremities showed nothing of note. Blood-pressure 125 to 80; red blood cells,

4,080,000; hemoglobin, 75 per cent.; white blood cells, 9500. Differential: neutrophile polynuclears, 56 per cent.; eosinophile polynuclears, 1 per cent.; large lymphocytes, 36 per cent.; small lymphocytes, 7 per cent. Urine negative. Blood Wassermann negative. An orthodiagram at this time showed the round heart of chronic myocarditis with an area of 130 per cent.

Rest in bed and forced diet were ordered. After an initial loss of two pounds his weight remained practically stationary until October 26. In this period he had occasional attacks of epistaxis. He gradually gained weight from this time until November 9, when he weighed 123 pounds. Because of hypertrophied tonsils tonsillectomy was done November 11, following which a septic temperature developed. Upon examination an abscess was found just in front of the posterior pillar of the fauces, and this was lanced. After several days of hot saline irrigations the temperature fell to normal. A roentgen ray of the teeth showed an apical abscess of the left lower first molar, and on November 26 this tooth was extracted, following which his temperature again rose to 104.4°. On November 28 the thrill and bruit over the gland had both markedly increased in intensity and his weight was 115 pounds. At this time he also complained of pain in his right ear. On the 28th and 29th he had several attacks of epistaxis. In spite of these difficulties he gained a little, and on December 10 he weighed 122½ pounds. He continued to gain until December 24, when his weight was 129½ pounds. On January 2 he developed an acute rhinitis, accompanied by severe headache, earache and sweating. Mastoid tenderness appeared on the right side, and on January 5 a paracentesis was done. The ear drained freely and was subsequently treated with hot saline irrigations. On January 15 he had shown marked improvement, but the temperature still showed some fluctuations, the maximum being 100.8°. The signs of hyperthyroidism were markedly diminished: exophthalmos had decreased slightly the tremor of the hands was by no means so marked as previously and the thyroid enlargement had practically disappeared. There was marked pulsation of the great vessels of the neck, but no thrill could be felt, and there was no bruit. He continued to improve until January 22, when he contracted influenza. His temperature rose to 102° and he complained of some stiffness of the right side of his neck. By January 28 his temperature had again returned to normal, and it remained so up to the time of his discharge. On February 5 exophthalmos was noted as being somewhat lessened, but lagophthalmos was still slightly evident. On February 10 lagophthalmos had practically disappeared. He was discharged February 21, there being at this time no neck signs save a very slight enlargement. He himself felt that the improvement in his condition was most striking. Following discharge he continued to improve, and on April 1 his weight was 185 pounds and he was feeling fine.

The course of these two cases makes it seem not unlikely that we have in them examples of infection, which either by direct invasion of the gland or by toxic action so affected the secretory tissue of the thyroid that subsequently the Graves's disease was very much improved. Whether this improvement can be regarded as the result of glandular exhaustion or actual loss of secretory tissue through damage is difficult to say. It would seem most probable that the latter explanation is the true one.

**Summary.** 1. As is well known, acute infections occurring during the course of Graves's disease usually cause a marked increase in the severity of all symptoms.

2. Sometimes, however, such infections apparently do injure the gland sufficiently to result in eventual alleviation of the condition.

3. Two cases of hyperthyroidism are cited in which complicating infections first caused a marked increase in the severity of the thyroid symptoms later followed, after the acute infection had subsided, by striking improvement if not cure. It is not improbable that the improvement seen is due to actual loss of secretory tissue through postinfectious sclerosis of the gland.

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## GLUCOSE TOLERANCE TEST IN CHRONIC VASCULAR HYPERTENSION.<sup>1</sup>

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I WISH to present briefly in this paper the results of 25 glucose tolerance tests done on 23 cases of chronic vascular hypertension. Hopkins,<sup>2</sup> Hamman and Hirshman,<sup>3</sup> Janney and Isaacson<sup>4</sup> and others have shown clearly enough that patients with diabètes, nephritis and certain endocrine disturbances cannot handle glucose taken by mouth as well as normal persons. Patients with chronic vascular hypertension can hardly be regarded as diabetics or nephritics, and as yet no endocrine disturbance has been proved in them. They, too, may show a disturbance in handling glucose. This type of case is, of course, very similar to the nephritic with hypertension. The element of retention of glucose, however, which complicates the interpretation of the glucose tolerance test in the true nephritic, apparently does not occur in the true chronic vascular hypertension

<sup>1</sup> Read at the meeting of the New York Academy of Medicine, April 1, 1920.

<sup>2</sup> AM. JOUR. MED. SC., 1915, cxlix, 254.

<sup>3</sup> Arch. Int. Med., 1917, xx, 761.

<sup>4</sup> Jour. Am. Med. Assn., 1918, lxx, 1131.

[illegible]

case. Undoubtedly the fundamental factors underlying the lack of tolerance for glucose in these conditions is the same. What these factors are we do not know. The 25 tests arranged as I have arranged them in the accompanying chart throw an interesting light on the subject of potential diabetes.

While following a large group of these chronic vascular hypertensive cases we noted that from time to time some of them showed a trace of sugar in the urine, occasionally enough to quantitate. Our curiosity was aroused to explain it. Were we dealing with cases of renal diabetes? While the evidence we have at hand is not sufficient to absolutely exclude this condition, it is practically certain that renal diabetes can play only an occasional part. Were we then dealing with mild diabetes? The occurrence of the sugar was so intermittent that it was obviously not practical to establish the degree of tolerance by any dietary test such as one would use in the diabetic. The glucose tolerance test of Janney and Isaacson was therefore used to see whether or not there was any disturbance of carbohydrate metabolism. This test, in its simplest form, consists in the determination of the fasting blood-sugar in the venous blood and the blood-sugar two hours after the ingestion of 1.5 grams of glucose per kilogram of body weight; 2.5 c.c. of water are used for each gram of glucose. In addition we determined the quantity of sugar present in a specimen of urine three hours after the glucose was taken and in the twenty-four-hour specimen. (The figures in the chart for the glycosuria during the test are for the three-hour period.)

In the chart on page 368 the dot represents the fasting blood-sugar, the circle and the blood-sugar two hours after the ingestion of the glucose. The normal difference should be 0.02 per cent. or less. Our cases are arranged according to the size of this difference, beginning at the left, where there is no difference, and moving gradually to the right, where the last case shows a difference of 0.22 per cent., eleven times the normal. A glance at this widening band of difference will show how these cases tend to merge into the typical diabetic reaction in this test.

In the line below the occurrence of glycosuria during the test is noted. A plus sign represents a trace. Two or more plus signs an amount sufficient to quantitate by the fermentation method, in the last two cases 4 per cent. and 2 per cent. respectively. Eight cases showed glycosuria during the test.

In the next lower line is noted those cases which showed glycosuria at times other than during the test—in all, 11 cases.

In the next lower lines are given the phthalein excretion and the blood-urea nitrogen, which, together with the two-hour renal test, which was done on each case, show normal renal function for all of these patients.

The systolic and diastolic pressures are shown in the line below and at the bottom the presence or absence of arteriosclerosis as demonstrable in the peripheral and retinal vessels. It may not be amiss to say at this point that the mere fact that no sclerosis of the peripheral vessels is observable does not exclude arteriosclerosis. The smaller arteries, which are perhaps more important than these larger ones, often show definite arteriosclerosis. The retinal vessels are the only small vessels that can be observed. These vessels are of particular importance in this disease, in that they offer us the only possible index of the small vessels of the various organs, especially of the brain.

In analyzing the results of the test we can see that the first 7 cases were not abnormal in regard to glucose metabolism, except that one showed a glycosuria during the test, No. 12568 showing 0.63 per cent. The remaining 11 cases, however, show well-marked variations from the normal, as indicated by the high blood-sugars after taking the glucose and by the very definite glycosuria in 5 cases. Surely one will admit that the last 2 cases—the first with a difference of 0.14 per cent. and a glycosuria of 4 per cent. and the last with a difference of 0.22 per cent. and a glycosuria of 2 per cent.—approach the typical diabetic reaction, if they are not actually diabetic.

There is no relation of importance between the height of the blood-pressure and the reaction in these cases. The differences in the glucose reaction could not be linked up in any way with differences in the amount of arteriosclerosis, although this may be a factor. I know of no method of measuring accurately comparative variations in the degree of sclerosis.

Two cases (9799 and 11,704) have had the test repeated. The results are of great interest in showing the variability of this glucose function. No. 11,704 showed an essentially normal reaction followed nine days later by a slightly abnormal one. No. 9799 showed (at the right of the chart) a markedly abnormal reaction. Several months later, however, her reaction was normal except for the occurrence of sugar in the urine during the test.

We know that these cases of chronic vascular hypertension are potential nephritics. Perhaps most of our chronic nephritics with hypertension develop from the purely vascular hypertensive case rather than from an acute and subacute nephritis. Are these cases potential diabetics too? My chart indicates that they are. The test of time alone will show whether they develop into true diabetics. Some of them will undoubtedly die from other causes before diabetes is definitely established, but perhaps a few may live long enough to give us the answer to this question.

The assistance of Miss Harriet Amory and Miss Janet Murphy in this work is gratefully acknowledged.



## SOME OBSERVATIONS ON CHRONIC ARTHRITIS.

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No attempt will be made at this time to discuss the classification of chronic arthritis. Certain features of the disease and of some individual characteristics of its subjects will, however, be brought out for consideration. The study was developed along lines suggested by the writer's<sup>1</sup> experiences in the poliomyelitis epidemic in 1916 and later among the meningitis cases in the army. These experiences brought out undeniably the circumstance that there was in both diseases a remarkable uniformity in certain anatomic characteristics of the patients. The attempt to analyze this similarity in appearance by comparing each person with a "normal" was unsuccessful, because in a mixed race the normal is quite indefinite. Consequently, recourse was had to the known endocrinopathies.<sup>2</sup> Each patient was observed with an eye to his possession of anatomic or physiologic characteristics which, though slight, might find counterparts in one or other of the endocrine disorders.

The great frequency of the disease arthritis in women is well known. Furthermore, it is often recorded that at the time of the menstrual period patients with chronic arthritis suffer either an exacerbation of their joint symptoms or are very much better. Many cases during pregnancy lose their joint pains about the fourth month. In addition to these observations the menstrual history of women with chronic arthritis describes irregularities of one sort or another; delays, periods of amenorrhea and frequently much pain.

While a considerable number of cases begin with large joint involvement the small joints of the hands have been the target primarily, and often, indeed, comprised the chief articular expression of the malady in its milder forms. The changes in the joints of chronic arthritis have been divided into two main groups, productive and atrophic, but radiographs show clearly that whether joint destruction, which is the criterion of the atrophic form, be present or not there is always increase in the bony structure. This expresses itself as an increase in the bone about the joints, often thickenings in the phalangeal shanks and especially in the terminal tuftings. These important structures assume an appearance extraordinarily like that seen in cases of pulmonary osteoarthropathy. It is also analogous to the appearance of the terminal tuftings and the phalangeal shank thickenings that are present in the well-known radiographic picture of the hand of the acromegalic. It may be well

<sup>1</sup> Draper, G.: *Acute Poliomyelitis*, Philadelphia, 1917.

<sup>2</sup> Draper, G.: *The Relationship of the External Appearance of the Body to Disease*, New York State Med. Jour. (not yet published).

to call attention here to the tendency of acromegalics to chronic bronchitis, bronchiectasis and emphysema—conditions which have been associated in turn with the terminal phalangeal changes known as pulmonary osteoarthropathy. Wright<sup>3</sup> reports one case of chronic bronchitis in which pulmonary signs ceased completely when the joint symptoms began, and another case in which the appearance of rales in the lungs was coincident with the onset of arthritis. One other feature which must be mentioned here in relation to the skeleton of these cases is found in the bones of the skull. Here in all five cases were found marked irregularities in the sella turcica (especially thickenings of the posterior clinoid process), all concerned with increased bone-production and an evident increase in the size of the sinuses or the density of the bone structure in the acral portions of the skull. In this connection it is of interest to record the report by Wright of a case of chronic headache which later developed chronic arthritis. The headache ceased with the onset of the joints.

The study of patients with chronic arthritis along the line of comparison with the anatomic characteristics of acromegalics brings out certain points of similarity in other parts of the body almost as striking as those found in the hands. In the five cases on which these preliminary remarks are based the modelling about the brow and eyes, facial bones and jaw is analogous to that of the acromegalic, to wit: prominent glabella region and supra-orbital ridges, high nose bridge and dental irregularities. All the individuals likewise showed a wide subcostal angle and in the male subject a tendency to the feminine distribution of fat and hair. The examination of the blood in these patients also shows consistently a tendency to low total leukocyte count, with the polynuclears diminished at the expense of mononuclear elements, a phenomenon commonly found also in the acromegaloid and Froelich types.

Previously more attention had been given to the thyroid gland in relation to chronic arthritis, especially by the French. Vincent<sup>4</sup> states that 68 per cent. of acute rheumatic fever have thyroid swelling, and believes that those who subsequently develop arthritis deformans have an associated, perhaps residual, insufficiency of the thyroid. The cases of our series have certain anatomic and physiologic markings, suggesting thyroid disturbance, such as dry skin, sweating palms, poor nutrition, nervousness and fatigability. Paul Claisse<sup>5</sup> has also reported the general "slowing down" of all functions in certain forms of chronic arthritis.

The sugar metabolism function of these individuals demonstrates

<sup>3</sup> Rheumatoid Arthritis, Canada Lancet, Toronto, 1911, lxx, 812.

<sup>4</sup> Rheumatisme et opotherapie thyroïdienne, Soc. méd. de hôp. de Paris, 1908, xxv, 677.

<sup>5</sup> Rheumatisme thyroïdien chronique, Soc. méd. de hôp. de Paris, 1908, xxv, 675.

an average or slightly diminished tolerance. In two of the cases there has been a very definite dull frontal headache following the ingestion of sugar. Several of the patients have shown a great craving periodically for candy, after eating which they developed a dull frontal headache. One patient, a male, with spondylitis, is a chronic candy fiend. An examination of the blood count following the ingestion of the glucose for the sugar-tolerance test shows no disturbance of the leukocyte count, except possibly a slight tendency to depress the total count. Several of these patients have described suffering from hives in childhood and occasionally in later life.

The cases of this series, each of which had been "through the mill" for many years in attempts to arrest or cure the disease, have recently been treated in desperation by the old and homely method of the stings of honey bees. While certain definite clinical improvements have supervened in these patients, some interesting observations about the effect of bee stings have been made. It is the chief concern of this report to consider the phenomena associated with the action of the bee venom rather than to discuss its therapeutic effects.

In the first place the bee sting produces a lesion locally which is the perfect replica of an urticarial weal; later on there is generalized diffuse swelling, with redness and heat, and pain and stinging sensation which resemble the lesion of acute rheumatic fever. In two cases it was observed that fading or almost healed sting reactions on one arm, of several days' duration, developed fresh erythema and swelling within a few hours after new stings were given on the other arm. In one instance, on the seventh day following the first stings, there arose about the site of the more recent lesions typical urticarial rose-pink blotchy eruptions. In addition to this the patient had a rise of temperature, with tenderness and swelling of the lymph nodes, the whole picture typical of a mild attack of "serum sickness." Adrenalin injected at this time caused the eruption on the arm receiving the drug to subside. But the eruption on the opposite arm, like the other symptoms, was uninfluenced. Medical literature contains numerous reports of severe symptoms and even death caused by the stings of bees. There is a striking uniformity in all the accounts. In practically every case acute and rapidly advancing swelling, syncope, weak pulse, oppression of breathing and often vomiting supervening, the edema may reach an extreme degree. No better descriptions of angioneurotic edema can be found than in these ancient records of the remarkable phenomena produced by the stings of bees and hornets. It is interesting that every case in which serious or fatal symptoms developed was stung on the face or head. At this point it is worth while calling attention to the reported chemical analysis of bee venom. Much work has been done both by J. Langer and more recently by F. Flury. The former author considers the venom an organic base precipitated by

alkali, giving alkaloidal reactions and remaining undisturbed by heat up to  $100^{\circ}\text{C}$ . Flury has carried the analysis of this base further and finds it to be a complex substance in which an indol derivative isolated as tryptophan, various fatty acids and bodies resembling saponin and lecithin have been found. None of the substances described are usually associated with the phenomena of sensitization and anaphylaxis, so that there seems for the moment to be some discrepancy between the biologic effects of bee venom

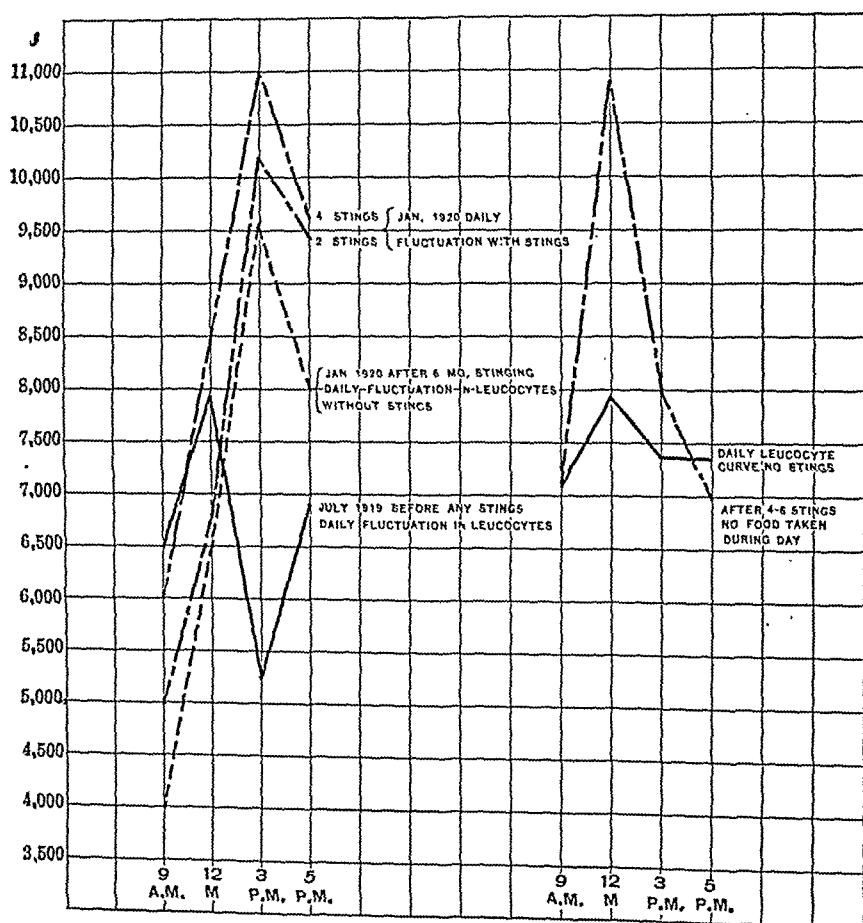


CHART I

and its chemical composition. Langer's work on the hemolytic power of bee venom and its ability to produce local necrosis exposes an analogy to certain snake venoms.

The white cell count of the blood showed interesting changes following the introduction of bee venom. Chart I shows the response of leucocytes to the venom in two cases. In the first case the solid black line indicates the diurnal curve obtained from counts taken at 9, 12, 3, 5 o'clock, before the patient received any venom. The dotted line shows the diurnal curve six months later, after

many stings and definite clinical improvement, on a day when no venom was given. The dash-dot curves show the immediate effect of the venom. In the second case the solid black line represents the diurnal curve taken at some time during the first two weeks after starting bee treatment. The dash-dot curve shows the extreme rise of the count immediately following six stings. All these counts were controlled, with special reference to the time of taking food and on the days from which the charts of the second case were taken the patient fasted all day. Very many observations were made during the year and all confirmed the fact that within fifteen minutes to half an hour after the introduction of the bee venom almost every case began to show an increase in leukocytes. The rise continued sharply for an hour or two and then fell off as rapidly. Some cases showed a delay of several hours before the rise set in. The total count is chiefly elevated, but there is also a definite increase of the polynuclears at the expense of the lymphocytes. This rise of the total count is not sustained but falls within two or three hours to the original level. Over a period of months, however, there seems to be slow, continuous and evenly sustained rise of the total count. In one case in which the bees were omitted for a period of three weeks the count fell back to its original level.

Clinically all the cases have shown a very definite improvement in their sense of well-being and in their appearance. In one case a menstrual disturbance which had frequently amounted to complete amenorrhea for as long as eight months completely cleared up. The periods were resumed and continued at normal intervals. Chronic puffiness of the eyes and ankles disappeared and the effect on the joints was also very noticeable. The subjective improvement was marked. One case had dull headaches following stings, but the joints were less affected by atmospheric changes than they had been previously. All of these patients were old stagers in the matter of knowing what real improvement was, and had been disappointed so often that they started out as complete skeptics, so that whatever value there may be in subjective improvement in the matter of pain and discomfort is worth more in this particular malady probably than in some others.

Just what the mode of action of the bee sting is at present is comparatively obscure, but the effect upon the blood count, the skin reactions and the reports of generalized edema and the temperature rise suggest acute protein shock analogous to the effects obtained by injections of many foreign proteins. Artificial bee stings composed of various dilutions of formic acid produce the same, though much milder, local effect than the true bee sting does and no constitutional changes. The indication that sensitization processes are concerned and the consideration of the analogy of the bony changes to those associated with pulmonary conditions led to inquiry for the presence of asthma, urticaria and eczema in the patients

# BEHAN: INTERPERITONEAL ADHESIONS

themselves or in members of their families. Chart II illustrates, in striking fashion, the intense predisposition to the disturbances under discussion, which runs through the family tree. Consideration of all these points leads to the conclusion that chronic arthritis represents a very profound constitutional disturbance in which forces analogous to those concerned in acromegaly

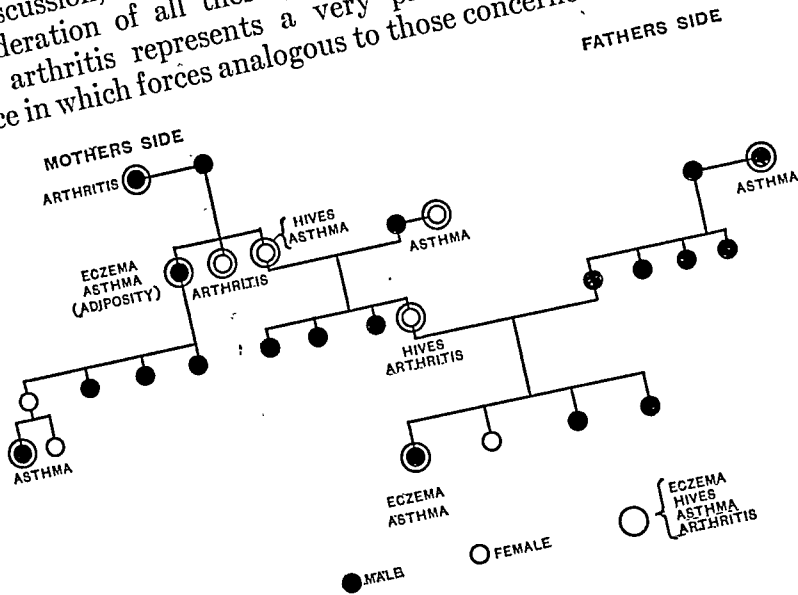


CHART II

and thyroid insufficiency are concerned. The family and personal history which arthritic patients give of hives, angioneurotic edema (bee sting effects) and asthma, and, in addition, the well-known feature of joint involvement seen in serum disease, all seem to indicate that there is a relationship between this whole group of phenomena and chronic arthritis.

## INTERPERITONEAL ADHESIONS, THEIR ORIGIN AND PREVENTION.

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- Three series of experiments on rabbits were made with three different purposes in view:
1. To define the origin and prevention of adhesive formations in the peritoneal cavity.
  2. To elicit the active cause of acute gangrenous (suppurative) appendicitis.
  3. To determine whether an opening in the bowel, made either by accidental traumatism or during an operation, may be closed

permanently by implanting a portion of another segment of isoperistaltic bowel into the opening, so that the serosa of the implanted bowel is sutured to the mucosa of the bowel at the margin of the defect; the defect is present, making as it were a plug to block the opening.

I shall confine this paper to a discussion of interperitoneal adhesions as produced artificially.

By experimental methods an attempt was made to produce interperitoneal adhesions: (1) By chemical irritation; (2) by traumatism of the serosa surface of the peritoneum; (3) by the action of bacteria or of sterilized cultures of bacteria (bacterial toxins).

After attempting to define which of the above processes was potent to cause adhesive formation, further effort was made to determine the extent to which adhesions could be restricted or inhibited by the application of lanolin and boric acid (5 per cent. boric acid in lanolin). By previous experiments it had been shown that this preparation had a restrictive action on the formation of interperitoneal adhesions.

It was also determined by the present series of experiments that in the presence of normal inflammatory tissue reaction the result of bacterial invasion, that lanolin and boric acid does not prevent adhesion formation. The cause of such failure evidently is that normally when the serosa is irritated by chemical means or is superficially destroyed by traumatism the lanolin and boric acid paste applied over the affected area acts as a protection to these areas for several hours, or until sufficient time has elapsed for the normal protective forces in the affected area to renew the serosa to such an extent that adhesions cannot be formed. If the serosa destruction is not repeated new endothelium forms and no adhesions form. However, if repeated destruction of the endothelium occurs at short intervals or if the destruction is continuous, as in inflammatory reactions, the protective action of the lanolin and boric acid does not continue sufficiently long for the new endothelium to form.

For adhesive formations between two adjacent areas of the bowel, or between the bowel and some other viscera or the peritoneal coating of the abdominal cavity, it is necessary that both opposing surfaces be denuded; or, if the two surfaces coming into contact with each other are not denuded, that they remain in forcible contact for a considerable period of time. How long a period of apposition is necessary I have not been able to determine. If such apposition is present, and if one of the apposing surfaces is denuded or is inflamed, the exudation which forms upon the affected surface will come into contact with the unaffected serosa of the opposite surface and will produce the same reaction in this area as in the affected surface.

If the two serosa surfaces have been injured and are kept in contact it requires only a very short period of time for adhesoin formation to take place. However, if neither of the two adjacent surfaces is injured, or if there is no inflammatory exudation present in the immediate neighborhood, adhesions will not take place between these two surfaces.

Chemicals such as tincture of iodine, carbolic acid, Dakin's solution, bichloride of mercury in strong solution, etc., will quickly destroy the frail endothelial cells on the serosa surface. Even when two adjacent surfaces come into direct contact and the serosa has been destroyed or injured, union will not take place if there is sufficient movement between the two apposing surfaces to inhibit a direct and intimate contact for a considerable period of time does not ensue. Exposure to the air, so that the serosa surface of the intestine was thoroughly dried before the bowel was returned into the abdominal cavity, did not cause adhesion formation (experiment of September 19, 1917).

Therefore from the experiments we have conducted it has been considered best, after operation in which considerable traumatism to the serosa surface in the abdominal cavity has occurred, to frequently change the position of the patient and at the same time to give some drug, such as eserine, which will stimulate the peristaltic activity of the intestine. Tympanites should be counteracted immediately. Heat instead of ice should be applied over the abdominal cavity.

As confirmative of the above opinions I shall review a few experiments in which an attempt was made to cause interperitoneal adhesions, and then after having determined that adhesions could be formed under certain conditions, I shall detail the results of attempts made, under similar conditions, to inhibit the formation of adhesions by the use of a heated paste of 5 per cent. boric acid in pure lanolin.

In these experiments it was noted that when inflammation was present in the peritoneal cavity that the lanolin had a tendency to collect in small, whitish masses and that adhesions would form the same as though lanolin had not been used.

This is exemplified in an experiment of February 4, 1918, when a small needle opening was made in the end of the appendix of a rabbit and some of the appendicular contents was expressed upon the surface of the appendix. Tincture of iodine was now injected into the appendix and also was applied to the appendix over the needle opening. This portion of the appendix and the adjacent structures were now covered with lanolin and boric acid.

At an operation performed on February 12, 1918, it was found that the appendix was inflamed, very red, with numerous adhesions at the extreme tip. They were very firm and extended for a short distance. The adhesions were freed and bled profusely. This



experiment should be compared with the one in which it was demonstrated that lanolin and boric acid applied in the absence of fecal contamination, over two adjacent surfaces to which tincture of iodine has been applied, can prevent adhesions. This protective action was demonstrated by the following experiment:

In a rabbit on February 4, 1918, tincture of iodine was mopped on the mesocolon to the left of the large colon. Lanolin and boric acid were applied over this area. At an operation on February 12, 1918, it was found that the area of the mesentery and bowel to which tincture of iodine had been applied and over which lanolin and boric acid had been smeared was free from adhesions. Tincture of iodine and lanolin and boric acid were again applied to this area. One month later the rabbit was again operated and it was found that adhesions were very marked over the entire abdominal cavity. It was also noted that there were masses of whitish material present in the abdominal cavity, collected mostly on the right side. Evidently the aseptic technic had been defective in this case, and inflammation, protective in type, had taken place, thus conserving the life of the rabbit. The lanolin and boric acid had not inhibited this protective inflammatory reaction.

The results in the above cases are confirmative of the results obtained in earlier work.<sup>1</sup>

In an experiment performed on December 25, 1917, two adjacent surfaces of bowel were swabbed with tincture of iodine, full strength. Approximation sutures were now placed so that the two surfaces were held directly in contact. No lanolin nor boric acid was applied. On December 28 the rabbit died from an acute inflammation, induced by artificially produced appendicitis. It was found that the areas of the bowel which had been treated with tincture of iodine and had been approximated were slightly adherent to each other. In another rabbit two adjacent surfaces of the bowel were denuded of their serosa by rubbing with the edge of a knife-blade, and over this lanolin and boric acid were applied, after first swabbing the abraded surface with tincture of iodine (full strength). The adjacent surfaces were found on December 25 to be adherent to each other at the lower end of the denuded area, beyond the area over which the lanolin and boric acid had been applied. The experiment added further proof of the potency of the lanolin and boric paste to inhibit adhesive formation, as the experiments show that tincture of iodine will cause dense adhesions when the bowel surfaces are held immovably in contact by suture and that lanolin and boric acid will retard adhesive formation even when the adjacent surfaces are denuded and tincture of iodine is applied.

The experiment of January 19, 1918, is further proof of the activity of tincture of iodine as a cause of adhesive formation.

In this rabbit tincture of iodine was applied to the serosa surface

<sup>1</sup> Report in New York Medical Journal, July 22, 1916.

of the mesentery of the large bowel and to the adjacent segment of the bowel. The viscera were then pushed back into the abdominal cavity on the left side and were covered with other bowel segments, so that the operated area was entirely separated from the wall and the appendix, which had been operated on at the same time. It was found on reoperating, February 10, 1918, that at the place where the tincture of iodine had been applied adhesions were so firm that it was necessary to cut them. There was considerable bleeding from the raw surfaces. The above experiment indicates that adhesions readily occur when two adjacent serosa surfaces of the bowel are irritated by chemical means and are then kept in contact. At this stage of our inquiry a very pertinent question to be answered was, Will direct and immovable contact of two serous surfaces, in the absence of traumatic or clinical irritation, be sufficient to cause adhesions? The result of such a contact is shown by an experiment of April 13, 1917. Two segments of bowel were sutured together so that a small pocket was present between them. On April 18 no adhesions were found except where the sutures had joined the two surfaces of the bowel together. At another place two adjacent surfaces were approximated, but into the pocket formed by this approximation three or four loops of a killed culture of colon bacilli were introduced; there was a slight amount of bleeding. It was found on April 18 that adhesions were present. Adhesions were also present in another case, where three or four drops of a killed culture of colon bacilli had been inserted into a pocket formed by approximating two serosa surfaces. Lanolin was also applied in this case and there were dense adhesions. Dead bacteria apparently are active in inciting adhesive formation. This is also shown by an experiment in which in one place several drops of colon bacilli were inserted where the bowel formed a loop and a pocket was present. On June 20, 1918, it was found that there had been present in this area a very severe reaction. In the entire lower part of the area were found dense adhesions, which could only be separated by cutting. Dead colon bacilli injected into the peritoneal cavity are very toxic, as is shown by the following:

One cubic centimeter of a three days' culture of colon bacilli, a subculture of the colon bacilli used in the above experiments, was injected into the peritoneal cavity of a rabbit. The dead bacilli were diffused around the peritoneal cavity by means of the fingers. The rabbit died suddenly in four hours.

In a rabbit operated April 28, 1917, an attempt was made to define the reaction following denudation of both sides of the adjacent serosa surfaces, and the smearing of lanolin and boric paste over the denuded areas. This paste, however, had hardened and did not make a perfect film. The abdomen was then closed. On June 16 there was a firm union between the two adjacent surfaces. In this instance the lanolin and boric acid had been hardened and did not

make a perfect film, and this apparently accounted for the adhesion formation.

In another place in the same rabbit, on April 28, two bowel surfaces were rubbed rather severely with gauze, but not severely enough to cause bleeding. The adjacent surfaces then were approximated and held in contact by linen sutures. No lanolin was used. Firm adhesions resulted and were found in the operation of June 16. However, there were no adhesions to the adjacent viscera.

To further define the tendency to adhesion formation an operation was performed November 6, 1917, and the adjacent surfaces of two segments of the bowel were brought together at *A*, but were not denuded. At *B* they were denuded of their serosa on one side and at *C* they were denuded on both sides. At *A* and *B*, two days later, no adhesions were formed, but at *C* both surfaces were adherent.

This experiment was a repetition of one performed on September 29, 1919. At this time three areas were approximated. In one neither of the two adjacent serous surfaces was denuded. In the second area only one was denuded. In the third area both surfaces were denuded. However, in this case there was a considerable deposit of blood between the two surfaces, due to perforation of a vessel in the serosa of the bowel. On reoperation, September 14, 1919, it was found that the bowel had become adherent to the abdominal wall. On attempting to remove it it was perforated in several places. The entire abdomen was contaminated with feces. The cause of the adhesion probably was an infection with streptococci, a very active culture of which had been injected into the appendix at the time of the prior operation. On eventrating the intestines it was found that the approximated bowel surfaces were very firmly adherent, except at the point where neither of the two adjacent surfaces had been denuded of their serosa. Even here, however, there were numerous fine adhesions. It was impossible to separate the two adjacent surfaces of the bowel in the other two areas.

This would indicate either that there had been infection from streptococci or else that the presence of blood between two adjacent surfaces had a tendency to cause the serous surfaces to unite to each other. The latter apparently is the most probable, because in this experiment the rabbit had no adhesions present in the peritoneal cavity, except in the area where the bowel had been interfered with and near where the abdominal incision had been made. If there had been a bacterial destruction very likely a generalized peritonitis would have occurred, and adhesions would have been present throughout the entire abdominal cavity.

Another rabbit was operated on November 19, 1919. The same procedure was carried out as in the previous rabbit, with the exception that lanolin and boric acid were introduced between the adjacent

surfaces. In this rabbit there was also an operation on the appendix. The rabbit died the next day because of a gangrenous appendix. There was a considerable amount of inflammatory reaction in the abdomen adjacent to and around the area where the bowel surfaces had been approximated. All the bowel surfaces were found to be adherent to each other. These adhesions were evidently the result of inflammation.

In a rabbit operated on October 11, 1919, two segments of the large bowel were approximated by sutures. The space between the two segments was now covered with tincture of iodine ( $3\frac{1}{2}$  per cent. strength) and the bowel was reintroduced into the peritoneal cavity. Some of the surface, which was covered with tincture of iodine, was permitted to come into contact with the lateral peritoneal wall, the iodine being spread considerably over the surface of the bowel. Five days after operation it was found that there were a few adhesions present between the bowel where it had been approximated by sutures. It was noted that while iodine had been spread over the two adjacent surfaces to a considerable extent, beyond the place where they had been approximated, the union between them had only taken place where they were approximated, and that it had not occurred between the lateral peritoneal wall and the surface of the large bowel, which had also been covered with tincture of iodine. In this case it was also noted that adhesions between the incision in the abdominal wall and the mesentery had been more pronounced than between the incision and the serosa of adjacent bowel. There also seemed to be some adhesions between the mesentery and the portion of the bowel which had been covered with tincture of iodine, so that one might conclude that the tendency for tincture of iodine ( $3\frac{1}{2}$  per cent.) spread upon both adjacent surfaces, with the bowel held in intimate contact so that it cannot move away, is to destroy the serosa.

However, when the bowel is freely movable and when it does not remain in permanent contact with the peritoneal wall, adhesions do not take place between it and the adjacent peritoneum. From this experiment it would seem  $3\frac{1}{2}$  per cent. tincture of iodine should not be used in the abdominal cavity unless it is desired to promote adhesion formation or unless two adjacent areas of bowel so treated can be kept separated.

As noted above, lanolin and boric acid had a tendency to inhibit adhesions when tincture of iodine had been applied. Lanolin will also inhibit adhesions when an intestinal anastomosis has been made, as exemplified in the rabbit operated on June 20, 1917, in which an opening had been made into a segment of the bowel. Into this portion another bowel segment had been sutured. On operation, November 6, 1917, no adhesions were present around the place where the bowel had been inserted into the lumen of a second segment of bowel.

From the above experiments it may be concluded that lanolin and boric acid tend to inhibit adhesive formation only in cases in which there is no inflammatory reaction present. The inflammatory reaction inhibits the potency of the lanolin and boric acid. Lanolin and boric acid will not always inhibit adhesive formation where two adjacent surfaces are kept in intimate and permanent contact after they have been denuded of their serosa. Also, in case blood is present between the two adjacent immobile surfaces, lanolin and boric acid will not prevent the formation of adhesions. Nevertheless, from the very fact, that lanolin and boric acid inhibit adhesive formation in most cases of minor traumatism to the peritoneal surface, also in cases of more severe traumatism where there is more or less free movement of the intestine (abdominal viscera), and in other cases where no inflammatory reaction has taken place, it seems that the lanolin and boric acid performs a very valuable function, and should be used in all cases in which interperitoneal adhesions have been separated and in other cases in which it is thought possible that adhesions may form. As a further means of prevention it should be so arranged that two raw peritoneal surfaces do not remain permanently in contact with each other.

**Summary.** I have used lanolin and boric acid in over three hundred abdominal sections and have noted no bad results from its use. In fact, patients after its use claim they have very little pain, and those who have had a previous abdominal section and are able to compare their sensations with those experienced after the previous operation are always pleased with at the greatly lessened pain which they experienced when lanolin and boric acid had been used. For this reason, *i. e.*, the relief of pain alone, the use of lanolin and boric acid is justified. It certainly produces greater ease in the very severe operative patients. I find it very beneficial in those patients who have developed adhesions around the cecum and ascending colon, either from a chronic appendicitis or as the result of some congenital defect by which stasis is present in the colon, and has resulted in a perityphlitis and pericolic adhesive formation. In such patients I use it very liberally and have had uniformly good results. I have also used it in several cases of recurring interperitoneal adhesions with gratifying absence of the former symptoms.

The presence of adhesions between the omentum and adjacent viscera or the omentum and the abdominal wall, where a previous operation has been done, is also a suitable indication for the use of lanolin and boric acid.

In using lanolin and boric acid, however, precaution must be taken that the lanolin secured is as nearly pure as possible. Most of the lanolin on the market is contaminated in various ways and frequently its interperitoneal use causes a very marked reaction, *i. e.*, an elevation of temperature and of pulse. It should also be sterilized three times on three different days, each time for a half hour at a

temperature of over  $212^{\circ}$ . Before being used it should be heated so that it is absolutely fluid; in fact, it should be applied very hot to the peritoneal surface. In this way it dries out the moisture of the peritoneum and at the same time sticks very firmly to it. It should not be applied upon a moist surface. The bowel should be dry before its application.

I have also used lanolin and boric acid rather successfully in tendon implantation and transference, also in cases in which it was necessary to liberate tendons from adjacent structures, the adhesions being due either to traumatism or to tenosynovitis.

I have been using this preparation for the last five years. I am very well satisfied with it, and feel that it does a great deal of good.

Lanolin and boric acid paste, of course, has its limitations, as I have stated. In the presence of inflammation it does not act. This is a valuable quality, because if it did inhibit adhesions, in cases of peritoneal inflammation, its use would be very dangerous. Adhesions are the life-saving structures in inflammation of the peritoneum. Another fact of importance to be remembered is that lanolin and boric acid paste does not absolutely inhibit adhesions between two adjacent surfaces, which are denuded of their serosa and are held in contact. Therefore, it should be the attempt of the surgeon to see that no two surfaces denuded of serosa come into and remain in permanent contact. The viscera at the close of an intra-abdominal operation should be so arranged, if possible, that long contact cannot happen, and, as a further precaution, the position of the patient should be such after operation that involved peritoneal surfaces will have a tendency to gravitate away from each other, for this reason also the position of the patient should be frequently changed. Drugs which have an active peristaltic action, either strychnine or eserine salicylate, should be exhibited in quantities sufficient to produce active peristalsis. Magnesium sulphate is also a very good drug, useful for this purpose. Any cathartic, stimulating intestinal peristalsis may be exhibited with profit.

As a further aid to peristalsis, where there is no danger of spreading an inflammation, we apply heat to the abdomen in the form of hot-water bottles, electric pads, etc., which are very beneficial in sluggish peristalsis. Diathermia is one of the most recent but perhaps one of the best means of stimulating peristalsis after operation.

## THE PRESENT STATUS OF EMPYEMA.

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IN this communication only those cases of empyema thoracis will be considered which are caused by the common pyogenic organisms—streptococci, staphylococci, pneumococci, etc.—and which follow most frequently ordinary pulmonic inflammatory conditions. An entirely different problem is presented when the lesion is due to other inciting organisms, such as tubercle bacilli or actinomyces.

In 1915<sup>11</sup> some studies on empyema thoracis were completed and published. The conclusions which were brought out at that time have since been abundantly corroborated, and some of them seem to have acquired much additional significance. It is of importance to recapitulate the latter and to compare them with our added knowledge.

"In the vast majority of the cases empyema is secondary to some other inflammatory lesion in the body." Approximately 11 per cent. of the cases in the 1915 series were described as being "primary" in the pleura, and the most predominating reason for the assumption was that it was not possible to demonstrate at any time the primary lesion to which the pleural suppuration was subsidiary.

The opportunities afforded by postmortem\* examination do not always lead to an accurate opinion concerning the mechanism of the early stages of the pleuritis. Except in those cases in which section of the lung demonstrates consolidated areas in anatomical relationship with the diseased area of the pleura, there are no criteria present upon which any judgment can be based. In the greatest number of the ordinary† cases of suppurative pleuritis the pathology, as demonstrated at autopsy, includes a localized intrapleural abscess of larger or smaller extent, bounded by thickened parietal and visceral pleural layers, on the pulmonary side of which the lung tissue shows no change from the normal, or only such superficial inflammatory, or compression, changes as would naturally be expected in a structure in direct and intimate anatomic

\* No conclusive evidence can usually be demonstrated at operation regarding the priority of the lung or pleura in a pathological process in which both are implicated.

† The extraordinary conditions are, of course, those associated with epidemics. In a subsequent part of this communication the streptococcus cases which formed a fairly large proportion of the cases in the last influenza epidemic will be discussed. I have the impression that outbreaks of primary streptococcus pleuritides which affect relatively large numbers of people have been known unassociated with any "influenzal" epidemic.

relationship with a pyogenic process; these are the comparatively late cases. Such findings are expected in the primary pleuritis cases, but could equally well occur in the cases in which a pulmonary condition had antedated the pleuritis and in which, prior to the time the examination was made, healing of the lung lesion had been completed and had been accompanied with the disappearance of any perceptible evidence of the original anatomic changes; this state of affairs, I am quite sure, is very common.

Apparently a primary pleuritis can occur in one of two ways: One of the two, and perhaps the much less common, consists of an absorption of bacteria by the lymphadenoid tissue of the lung from the inspired air, with a consequent reaction in the pleura alone. Evidence toward this assumption was presented by Grawitz,<sup>4</sup> Arnold,<sup>1</sup> Heller<sup>5</sup> and Netter<sup>8</sup> in the period from 1890 to 1897, but since that time no additional proof of any kind has appeared in the literature. My own studies have led me to believe that under ordinary conditions this mechanism must be an exceedingly rare one, if it ever operates at all.

The second mechanism concerns itself with the phenomena associated with a temporary bacteremia. Organisms find their way into the blood stream, having gained an entry through the respiratory (including tonsils and adenoids), gastro-intestinal or genito-urinary tracts; and for some reason, which may not be apparent at any given moment, the pleura forms a fixation-point for the bacteria as these are filtered out of the circulating blood and an empyema results. Probably this mechanism functionates with many other similar or allied conditions; very possibly, too, it operates in the first of these two methods. Under such conditions it is very likely that the responsible organisms show an elective affinity for the pleural membrane. At the present writing it seems to me that no other available theory is adequate to explain the almost simultaneous occurrence of relatively enormous numbers of cases of primary pleuritis under epidemic conditions.

Over 90 per cent. of the empyemata one meets with are secondary to other immediately preceding conditions. It cannot be over-emphasized how important this observation is. In this respect the term empyema holds an exactly parallel place with the term peritonitis: neither of these expressions conveys a total concept to the clinical mind unless it be immediately modified by an indication of the primary inciting condition. The primary conditions can be roughly grouped into (1) the meta- or postpneumonic empyemata; (2) those occurring by continuity from a neighboring perforating abscess, and among these abscesses of the lung take first place; and (3) the metastatic forms following a focus of suppuration at a distant point or taking the form of fixation abscesses in the course of established and continuing bacteremias.



1. The empyemata with which one meets most commonly are those following pneumonia. In children a form occurs in which both pleura and lung simultaneously become infected and involved. In adults this form is rare, and, as far as one can tell, the usual course of affairs includes a definite progression from a pulmonary inflammation to a pleural involvement. Rosenbach<sup>12</sup> was the first to suggest the probability that many of the meta- and postpneumonci empyemata are directly induced by the rupture into the pleural cavity of small superficially placed pulmonary abscesses resulting from foci of liquefaction in the consolidated portions of the lung. The difficulties in adequately settling this point, especially as to the frequency of its occurrence, are apparently insurmountable; but what evidence we have seems increasingly to show that this mechanism is perhaps the most common, if not the only one, by which the ordinary forms of meta- and postpneumonic empyemata make their appearance. In a number of instances I have been able to demonstrate these abscesses on the operating table. One of these was in a fresh case of empyema; the other was found during the course of operation for the closure of an old thoracic fistula: in both of these in exploring the visceral surface of the empyema cavity the finger was caught in a small round hole which led into the pulmonary parenchyma. The observation of Rosenbach<sup>12</sup> is also corroborated in the report of the U. S. Army Empyema Commission<sup>3</sup> in the cases which occurred at the camps during the epidemic, small abscesses, which often were multiple, were repeatedly found at autopsy in the lungs, gathered at their peripheries and directly under the visceral pleura.

These cases should not be conflicted with any of the forms of empyema in the second group—empyema cases complicating frank pulmonary abscesses.

Meta- and postpneumonic forms of empyema form about 69 per cent. of the total number of cases encountered.

2. About 2 per cent. of the empyema cases under ordinary circumstances complicate abscesses in the immediate neighborhood of the pleura. This group includes only those which are formed by direct extension or rupture of the suppurative process. Very few of these, indeed, are derived from the subdiaphragmatic space; the very largest number are derived from the rupture of pulmonary abscesses. The latter form an important group of empyemata. The mechanism in these cases is quite simple, and it is possible to distinguish two varieties. In one of these there is a comparatively acute abscess formation with soft, non-demarcating walls, frequently multiple, commonly with few or no physical signs, and very liable to cause perforations between the non-adherent visceral and parietal pleura; the latter accident becomes associated with a sudden increase in the severity of the symptoms and the clinical picture becomes associated with, and characterized by, high fever, marked dyspnea

and cyanosis and other signs of a high grade of intoxication. The picture is that of a hyperacute pneumothorax. Pathologically these abscesses are noted by the absence of surrounding areas of induration. The resulting empyema involves, practically, the entire pleural cavity; the exudate is distinctly purulent, rather thin and frequently sanious, very foul and very toxic. As far as I know almost every case of this kind goes on to a fatal issue.

The second variety includes the chronic lung abscesses. The most characteristic of these are the foreign body intrapulmonary suppurations which follow aspiration of a fragment of tonsillar tissue during a tonsillectomy. Anatomically the lesion consists of a central cavity containing foul-smelling, brownish-red, grumous pus in which a multitude of organisms flourish; a limiting granulation membrane of firm consistence and a wide surrounding area of induration merging into pulmonary tissue in which fibrosis, secondary bronchiectatic dilatation and atrophy predominate. The lesion may be single or multiple and with it an advanced grade of suppurative bronchitis is associated. An adhesive pleuritis is almost the rule and is usually limited to the area of lung involvement. Empyema is less common; a general empyema is rare and occurs in those very exceptional cases in which no pleural adhesions have formed. The empyemata which are found are comparatively small and localized and the mechanism of their production becomes apparent from the anatomic structure in which one wall of the cavity is formed by much thickened parietal pleura and the opposing wall by suppurating membrane based on pulmonary parenchyma (pleural vomica). A bronchial fistula is always present. Clinically these are characterized by a prolonged period of illness, by a distressing cough, by fetid and profuse purulent sputum, by the evidences of progressive general deterioration and of local pulmonary involvement, and by characteristically definite roentgenographic pictures.

This type of empyema is illustrated by the notes of the following case:

In a man, aged fifty years, a lobectomy was done for a chronic lung abscess. The description of the pathology, as demonstrated at operation and by study of the specimen removed, is as follows: The lesion was present in the lower right lobe. The anterior, mesial and diaphragmatic surfaces of the lobe are free from adhesions. The latter are, however, present at the postero-internal border of the lung as far forward as the ligamentum latum pulmonum and for the entire extent of the latter from the pulmonary hilum to the base. In this location there is an empyema cavity containing several ounces of thick, yellow pus. The mesial wall of the abscess was a much thickened parietal pleura lining the reëtrant angle formed by the bend of the ribs and posterior mediastinum; the outer wall was pulmonary parenchyma in which the open ends of a number of bronchi of the second and third order were easily and distinctly

visible. The empyema lay for the most part within pulmonary parenchyma.\*

The demonstration of a bronchial fistula furnishes indubitable evidence of the presence of a suppurative process in the midst of the lung tissue. In the great majority of such cases the presence of the fistula is to be interpreted as proof of the priority of the pulmonary process, to which the empyema is subsidiary. In the lung-abscess-empyema cases the communication is frequently multiple, is usually direct and extends almost always into one or more fair-sized bronchi of the second or third order; the usually profuse and foul sputum, present before operation, resembles in all particulars the pus of the abscess; but it immediately disappears following the adequate drainage of the pulmonary abscess and reappears directly the drainage is interfered with from any accidental or purposeful cause. Healing is tedious and prolonged, and most often the bronchial fistula is an insurmountable obstacle to the closure of the thoracic sinus until, and perhaps even after, a radical operation is done. In those empyema cases which are subsidiary to the small superficial pneumonic abscesses (Rosenbach<sup>13</sup>) that rupture into the pleura a communication with the bronchial tree is not always demonstrable; in much the smallest number a communication makes itself apparent when, for one or another reason, a fluid irritating to the respiratory tract is introduced into the empyema cavity. The fistula may be tortuous and is narrow, and communicates usually with one of the smallest-sized or terminal bronchi. The amount of infiltration around the sinus tract is at a minimum, the tissues are soft and pliable and have a tendency to fall together; facilities for healing are most favorable in these cases, and it is exceptional for the communication to cause any extraordinary prolongation of the cicatrization of the wound. Characteristically the amount and physical appearances of the sputum is independent of the contents of the empyema cavity, has no resemblance to the wound discharges and depends for its production on any associated bronchitis which may be present or upon the liquefaction of the pneumonic exudate which had antedated the empyema.

In only a minority of the cases of empyema complicated with bronchial fistula is the evidence sufficient to indicate that the communicating sinus had resulted from the rupture of the empyema into some part of the bronchial tree. Such, for instance, would be so when an unrecognized liver abscess perforates through the diaphragm and discharges through a bronchus after having first created a subsidiary abscess in the intrapleural space; these occurrences, while quite well known, are relatively infrequent. With simple empyemata the discharge of pus into the respiratory tract is extremely rare, and probably when such an accident occurs it

\* Private records.

indicates the rupture of a coexisting, and perhaps unrecognized pulmonary focus. The experiences which I have had seem to show that the intrapleural abscess discharges much sooner on the skin (empyema necessitatis) or remains practically in an unchanged state except for the progressive thickening and even calcification of the limiting membrane. The prevalent beliefs in regard to accidents of this kind with simple empyemata seem to be exaggerations of the actual facts.

I have, personally, seen only one case in which an empyema ruptured into a bronchus. This was a woman who was admitted into the hospital on the service of Dr. Libman. An empyema was demonstrated and the pus was removed by aspiration as a preliminary measure. Several days later the patient was transferred to the surgical side (Dr. Elsberg's service) for operation; her condition was excellent at that time. As the patient was put upon the table for operation she very suddenly began to show signs of pulmonary embarrassment and within a very few minutes there was a marked edema of the lungs; she was deeply cyanosed and complained of a choking feeling. Under vigorous stimulation she was tided over the emergency and within a few hours began to bring up in the sputum moderate amounts of pus demonstrating beyond question that the purulent focus had ruptured into a bronchus. I believe that a lung abscess was present which had, primarily, caused the empyema, and, secondarily, had ruptured into the bronchus; the presence of the lung abscess had been suspected from the clinical manifestations by the medical men before the transfer of the patient to the surgical side.

It is a different matter with the frank lung abscesses; perforation into the bronchial tree is almost the rule with partial, or complete, drainage of the pus in the sputum.

3. Metastatic empyemata are very common and comprise between 4 and 5 per cent. of the total number of cases ordinarily seen. It is very probable that the mechanism of their production is very intimately connected with the lodgment of infected emboli within the confines of the pleura derived from the original source of infection. It is less common for empyemata to complicate the bacteremias in which no localized focus can be demonstrated clinically; usually there preëxist foci of suppuration from which the bacteria-carrying emboli are derived. The same question arises with these cases as to whether the secondary process in the pleura is primary in the pleura or is in its turn subsidiary to a superficial lung abscess. It seems more rational to assume that the emboli lodge in the capillaries of the lung near the surface and, after liquefaction of the focus has occurred, the latter ruptures into the pleural cavity with the resultant empyema formation. The same difficulties in proving this point are present and in the few cases of this kind which I have had the opportunity of seeing postmortem the stage of the process

was so advanced as to make the elucidation of the question at issue impossible.

Metastatic empyema occurs most commonly after suppurative conditions in the lower abdomen and pelvis—postpartum sepsis, diseased adnexa, suppurative appendicitis; less frequently it follows thrombosed hemorrhoids, middle-ear suppurations or abscesses in other organs. In looking over my records I was surprised to see that I had never observed an empyema to follow a furunculosis.

Unless there is present an established bacteremia the prognosis for metastatic empyema is not any more grave than for other forms of suppurative pleuritis.

Conditions during the epidemic of 1918 and in the various army camps, although peculiar, fitted in with our previous knowledge. The empyemata seem to have followed one of several types.

1. The cases resembling those ordinarily seen and following pneumococcus pneumonias of the lobar type (Alabama drafts at Camp Custer and Camp Upton). The proportion of cases developing empyema was not out of the ordinary and in the Camp Upton cases (Brooks and Cecil<sup>2</sup>) it is put at 11 per cent. The trouble seemed to be that unexpectedly large numbers of the men came down with pneumonia; the pathological lesion itself or the complicating empyema showed no new phenomena.

2. In some of the camps (Camp Custer and Camp Sevier) there were large numbers of men who fell ill with measles. In such closely crowded quarters the measles assumed epidemic characteristics and an unexpected severity. That in turn large numbers of the men, ill with the exanthem, developed pneumonias of various kinds was to be expected; such a progression is common in civil practice when measles spreads in epidemic form in the wards of a hospital, and especially among adult patients. The clinical experience of the camp hospitals parallels that seen in the civil hospitals: the primary exanthem might be mild or severe; the complicating pneumonias were many, were either of the lobar or lobular type, were marked by the evidences of marked toxemia, were frequently complicated by empyema and the total mortality was very high.

In some of the measles cases at Camp Custer (Beals, Marlow and Zimmerman) the pleuritis occurred without any demonstrable preceding lung involvement. In a few of these lung infiltrations were found postmortem surrounding the intrapleural abscesses, but the physical characteristics of these and especially their distribution seemed to furnish sufficient proof of their secondary and subsidiary nature. Some of the cases of empyema following measles, which I studied in the 1915 series, were of this type.

At Camp Upton (Brooks and Cecil<sup>2</sup>) pneumonias frequently followed tonsillitis or other mild infections, and these, in turn, were complicated by considerable numbers of empyemata.

3. The most peculiar cases were those due to the "influenzal"

infection: The clinical pictures were characterized by a fulminating overwhelming of the patient by a tremendous toxemia and in the early stages of the epidemic this was so marked that large numbers of the patients died before any localizing process could form. Then, as the virulence of the epidemic abated somewhat, localizations were made out in the pleura more and more frequently; these assumed the characteristics of pleural effusions. The toxemia was still extraordinary and the patients died before the effusions could become definitely purulent. Very few empyemata were encountered in the early months of the epidemic for these very reasons. Toward the end of the epidemic empyemata began to appear: the virulence of the infection was at its lowest; the patients did not die so quickly; opportunity was afforded for the full development of the pathological process and the longer intervals were conducive to the slow transformation of a pleural effusion, heavily charged with organisms usually of the streptococcus group, into a frank pyothorax. The mortality was still high; the deaths occurred rather early and were due to the initial illness and the character of the infection with its marked toxemia.

Postmortem examinations were frequently disappointing. The pleuræ showed the lesions of fibrinous or serofibrinous pleurisy. The lungs showed patches of bronchopneumonia or the process involved an entire lobe. The bronchopneumonias of streptococcus origin were of a peculiar organizing type and were especially prone to undergo liquefaction and form abscesses (McCallum). Fairly often the lungs were free of any change. These last cases came nearest to the classification of primary pleuritis. Undoubtedly the infection in any case was blood-borne and temporary or more prolonged bacteremias existed to which the pleuræ, or pleuræ and lungs, were points of fixation.

The pleuritis cases of this group have very marked resemblances to similar cases which occurred in previous epidemics. I quote rather freely from Leichtenstern's monograph on "Influenza" in Nothnagel's *System*. "In previous epidemics there were numbers of severe, mostly fatal cases of acute primary 'grippe-pleuritis' which made their appearance almost simultaneously with the appearance of the epidemic. The clinical course began with chills; almost immediately thereafter there was a high, continuous fever, extreme dyspnea and marked cyanosis. In a very short time a rapid accumulation of pleural fluid took place which not infrequently was bilateral. The fluid was thin, turbid, seropurulent and of a yellowish color. In repeated postmortem examinations it was definitely proved that these were primary pleurisies without any coexisting inflammatory infiltration in the lungs. In the exudates streptococci were often found in pure culture. As the virulence of the infection subsided empyemata became frequent."

**Exploratory Aspiration.** In previous years this method of exploring the chest for fluid, or of substantiating the diagnosis of effusion, had reserved for itself a paramount place. In spite of the fact that certain dangers attend its use, aspiration is of such value as to make one disregard them; and, to be sure, these occur very rarely, especially those which lead to untoward results. The most unfortunate of the latter is the occurrence of sudden death. The explanation of these reflex phenomena is most obscure.

As the cases present themselves it is found that the needle is most successful with the larger empyemata, especially those in which more or less total collapse of the lung has occurred. The procedure is, however, most valuable in the cases of localized collections of pus, since the physical signs are frequently inconclusive, both as to the presence and topography of the abscess cavity, while the clinical course strongly suggests the presence of a pus focus within the thorax. This is particularly so in the localized empyemata restricted to the upper areas of the chest, both in front and in the axilla, or in those confined within the borders of the pulmonary fissures. Particularly baffling are those within the axilla: it frequently happens that aspiration is practised in the usual areas, posteriorly, corresponding to the midscapular line, and in several different interspaces with negative results, while a little farther outward, toward or within, the axillary confines, purulent fluid would be produced. In actual practice it is always advisable to insert the needle in the very center of the area thought to contain fluid; toward the outer borders of the latter the layer of fluid may be thin and the needle is very apt to penetrate entirely through the fluid-containing space and to project beyond into the lung parenchyma, of course with negative results. One is frequently chagrined when, after having a great deal of difficulty in locating the pus with the needle, and after finally locating what is seemingly a small collection at some unusual and not easily accessible point, one discovers at operation that the empyema is of very large proportions thoroughly ample to cover and include every one of the aspiration areas. The reason for this difficulty is obvious from the foregoing statement.

A number of other sources of error are present in the practice of aspiration. In a number of the cases several loculi of fluid are present in the chest, and while one or several of these contain purulent exudate, another or others contain serous-like fluid (*mantelergüsse* of König); whenever pus is strongly suspected and clear fluid is withdrawn it is advisable to repeat the procedure at a different point in order to make absolutely sure that this snare is avoided.

In other cases the source of error lies in the withdrawal of pus when no empyema exists. On a number of occasions on the medical side of the hospital, and especially in children, the stage of resolution of a pneumonia was accompanied with symptoms resembling very

strongly those associated with purulent foci; aspiration having been practised purulent fluid was withdrawn. When transferred to the surgical side for operation the use of the needle failed to substantiate the presence of fluid of any kind\* and further observation was followed by complete defervescence and spontaneous cure. It is quite likely that in these cases the needle entered a large bronchus and withdrew some of the bronchial secretion, or possibly some of the liquefied pulmonary exudate was sucked up into the syringe.

Very difficult of distinction are the purulent collections in intimate relation with the diaphragm, and with the needle alone it is frequently very difficult, if not impossible, to decide definitely whether the pus is situated in the pleural cavity or in the subdiaphragmatic space.

**Roentgen Ray.** Much more accurate work can, however, be done with the roentgen ray. The diagnosis of fluid can be accurately made in the largest percentage of the cases examined. In those with collapse of the lung the roentgenographic shadow is usually diffuse and covers either the entire side of the chest or its lower half or two-thirds; in these the advantage of the roentgen ray over the exploring needle is not so obvious as in those about to be described, inasmuch as it is extremely improbable for one to miss the fluid in aspirating. The superiority of the roentgen ray over the exploring needle is, however, pronounced in all cases of localized empyemata whether the cavity be relatively small and obscurely placed or whether it be limited to one of the aspects of the thoracic wall. In the former the feasibility of reaching the cavity with the needle is at a minimum and very often it is merely a matter of luck whether one succeeds in entering the cavity at all; the roentgen ray, however, gives an accurate picture of the size, the location and the relative anatomic relationships of the pus cavity, and reaching the latter with needle or incision is then a matter of comparative ease and of almost mathematical precision; stereoscopic plates are invaluable and very essential for this purpose. In the larger localized empyemata the same advantages are still present though not to such an extreme degree; much useless aspiration is, however, avoided. The manifest superiority of the roentgen ray is illustrated in the notes of the following case:

A young man had gone through a severe lobar pneumonia, and having passed the critical stage was apparently on the road to complete recovery. Fever, however, recurred and with a progressive deterioration in the general condition, a continuing loss of weight and a persistent cough, it was strongly suspected that pus was present somewhere in the chest. Repeated aspirations were negative until finally the pus was located in the axillary space by the medical consultant. A roentgen-ray picture had been taken but

\* In a case of this kind the roentgen ray would be of tremendous help.



had not been properly interpreted. When I came to operate upon the patient I was able to point out the location and boundaries of the empyema cavity in the roentgenogram and to show that with proper interpretation the pus could have been reached on the first aspiration.\*

The delimitation of the empyema cavity by roentgenographic study has been of particular help in establishing beforehand the most advantageous point for drainage; the site of the incision can then be accurately planned. The notes of the following case are instructive:

A boy, aged eighteen years, had been operated upon for a post-pneumonic empyema. There had been a great deal of trouble in finding the pus with the needle, but, finally, it had been located in the lower part of the right chest very far forward. The incision, which was made, corresponded to about the level of the sixth rib and was entirely in front of the anterior axillary line. Operation was, however, followed by a continuance of the fever. When I came to see the patient I was shown the roentgenograms and, even before examining the patient, I was able to point out clearly the entire boundary of the empyema cavity, to show that the pus had been reached at the most anterior and inferior part of its extent and that the entire cavity lay behind the line of incision. As the patient lay on his back in bed the drainage opening was at the topmost extremity of the cavity; retention was, of course, present, accounted for the persistence of the fever, and necessitated a second incision posteriorly, the planning of which could be accurately done before operation from the roentgenographic pictures. All of this could have been avoided by correct reading of the plates originally.\*

The use of the roentgen ray affords another advantage in that frequently other unsuspected lesions are demonstrated in the picture. Perhaps the most important of these are the presence of associated pneumonic foci in the same or opposite lung. The question of whether a general anesthetic can be safely employed or whether one must have recourse to local anesthesia can then be decided much more easily and on definite criteria. The physical signs of such "silent" patches are indefinite and inconclusive and are not prominent enough to attract one's attention while examining the chest; frequently these small patches give no physical signs at all; they are, however, usually easily demonstrable in the roentgenographic pictures. A similar observation was made by Whipple several years ago; writing from the Presbyterian Hospital he pointed out how commonly postoperative pneumonias would go unrecognized because of the absence of any conclusive physical signs, if it were not for the roentgen-ray evidence. In my earlier experiences I remember

\* Private records.

several occasions when the thoracotomy was very promptly followed by an exacerbation of symptoms manifestly due to an area of pulmonary consolidation; undoubtedly this had found its origin in an unrecognized, silent and perhaps defervescing patch which had been stirred up into renewed activity or had been effectually spread by the irritating anesthesia.

In exceptional cases the etiology of an unexplained empyema is clarified by the roentgen-ray studies. A very interesting case is the following:

In a man of fifty years the predominating symptoms were a continued fever and a productive cough. Repeated exploratory aspirations of the chest were negative until finally some clear fluid was withdrawn; later a thoracotomy was done. An abscess was reached presumably in the midst of the lung and drainage was instituted; the discharge from the wound resembled the purulent sputum. Drainage continued unchanged for months. Roentgenographic pictures were repeatedly made, but had not succeeded in clearing up the underlying condition. Finally in one plate a gap was noted in the dorsal part of the third rib near its bend and angle which the radiographer interpreted as a new growth. Subsequent plates showed the defect to be increasing in size. The interpretation of the clinical picture was now easily made; the man had a tumor of the lung; this had involved the pleura, induced an effusion and the latter had become infected; the rib was the site of a metastatic growth or had become involved by direct extension of the tumor.\*

**Treatment.** The treatment of empyema is not difficult in theory but extremely difficult in practise. It involves principles established for many years. Necessarily it divides itself into that before operation, during operation and after operation.

Every empyema that one sees has gone through a stage in which the exudate was a relatively clear fluid, which, as time goes on, shows a progressive turbidity and passes finally into the stage in which the exudate is frankly purulent. As a general rule the fluid is heavily charged with bacteria and the abundance of the latter varies inversely with the length of time since the onset of the effusion; the longer the fluid remains in the chest the greater tendency there is for the bacteria either to disappear or to lose in virulence.

During the recent epidemic it rapidly became apparent that whenever the cases were operated upon very early—and this usually meant as soon as fluid accumulated in the chest—an appalling mortality resulted. Later it was learned that a policy of abstention from operation in the early periods of the pleural effusions was followed by vastly better results and that the proper time for operation only came later when the exudate was distinctly purulent, when the initial toxemia had abated or had been overcome, and

\* I am indebted to Dr. Elsberg for these notes.

perhaps when the original pneumonia had disappeared. All of these facts are not peculiar to the epidemic; they are equally true of the ordinary cases. In the communication made in 1915 this condition of affairs was dwelt upon and it was pointed out how the mortality seemingly became lower and lower the longer the pus was retained in the chest. The ambiguity of the situation was also pointed out at that time, inasmuch as notoriously bad results are obtained whenever the condition is neglected and the purulent collection is undisturbed for extraordinary lengths of time; the moment for operation comes only some time after the appearance of the intrapleural process and permits of no excessive delay; the timeliness of the surgical interference is easily apparent to the clinician. A similar observation had been previously noted by Werner and the superiority of comparatively late over early operation has also received the confirmation of the Empyema Commission.

It is not definitely settled just why the initial period of a suppurative pleurisy should carry with it agencies which contribute an excessive danger to an open drainage of the chest. A number of factors seem to be present: (1) The dangers of an open pneumothorax associated, perhaps, with the spread of the infectious process to other uninvolved portions of the pleura; (2) the risks of a further compromise of lung tissue leading to a dissipation of the respiratory function until the normal reserve is exhausted to the danger-point; (3) the absence of adhesions and the failure to fixate adequately the mediastinum so that "flapping" takes place; (4) the excessive toxicity of the exudate, the increased facility afforded by operation for absorption and the inadequate preparation of the human organism in the matter of necessary antibodies to overcome the toxemia; (5) the presence of the primary illness, especially a pneumonia, still in an active state; (6) and, lastly, and perhaps most important, and perhaps the only reason, the added insult of any-operative procedure—especially one resulting in an open pneumothorax—with its unavoidable shock to a patient whose resistance, because of all things considered, is at an extremely low, if not at the lowest, level. In any individual case the correlation of all of these factors working at the same time, or the operation of any one, or any group, of them is not only possible, but extremely probable if surgical interference is undertaken at an inopportune time.

During the epidemic these facts were emphasized much more strongly than would ordinarily be possible. Preliminary aspiration of the chest as a therapeutic measure has therefore grown in favor, and it has been found advisable to repeat the evacuation of the fluid as often as the general and local signs of the patient make the indication. The chest is best emptied with some form of suction apparatus—a Potain apparatus is excellent—and as much fluid as is possible should be withdrawn; a large caliber needle facilitates

matters very much. The evacuation of the fluid is usually promptly followed by an improvement in the pulse and general appearance of the patient. Within a few hours there is an appreciable drop in temperature; in many the normal level is reached. As the fluid reaccumulates the temperature rises again; sometimes the interval between aspirations may extend to several days. A recrudescence of fever is a very good guide for the repetition of the procedure.

Repeated aspirations are usually followed by rapid improvement in the general condition of the patient. This may cause difficulty in giving the patient an unwarranted sense of cure from the purely temporizing measure; in several patients operation was, therefore, refused at the proper moment, and permission to do so was only obtained at a comparatively late interval, when the initial benefits derived from the aspirations were replaced by other disadvantages, due to the extraordinary time the pus was allowed to remain in the chest; in one of these patients return to the hospital and operation was only acceded to after the empyema had perforated through the chest wall. It is well, therefore, to explain primarily to the patient, or to the latter's family, that the aspiration is only a temporary measure and that operation is being postponed for the sake of the added safety which the temporizing measure affords.

Preliminary aspiration has been found very satisfactory for tiding the patient over the dangerous intervals until the establishment of an open drainage of the chest is fairly safe. The criteria for determining the latter point are rather crude and include the physical appearances of the exudate; the general objective signs—temperature, pulse, etc.—pointing to a diminution of the initial toxemia; and improvement in the physical signs indicating, as far as one can tell, an appreciable resolution or disappearance of the pneumonia when the latter is the primary illness. Operation should not be done until the fluid is very purulent and until the toxemia has completely disappeared.

Very rarely repeated aspirations result in a disappearance of the exudative process and an actual cure. In my own experience this has occurred only in very young children and infants. In actual practice such a small assurance of permanent cure is offered by this method as to make the possibility negligible.

The question of whether or not infection can be spread during operation to healthy portions of the pleura is very important from the surgical point of view. As one sees the cases of empyema in the hospital they fall readily into one of a number of groups.

1. The empyema is a localized abscess and, compared with the total size of the interior of one side of the thorax, is relatively small. The abscess is well walled off, the adhesions are fairly strong and manipulations must be accompanied with the exhibition of considerable force before these will rupture. If the condition has existed for a considerable length of time—several weeks—the adhe-

sions are very firm indeed, much firmer than any adhesion ever seen in the abdominal cavity, and even at postmortem examinations it is next to impossible to tear these apart; almost always the pulmonary parenchyma ruptures before the scar tissue in the pleura gives way.

2. In the second group the lobes of the lung on the affected side have collapsed and have become fixed in place in a more or less shrivelled state in the interval formed by the curvature of the ribs and close to the spinal column. The degree to which the lungs have collapsed may be extreme or may be at a minimum; in the former the thoracic cage is practically in its entirety an abscess cavity; in the latter the cavity is rather shallow, although it extends from the upper to the lower limits of the thorax and is most frequently in relation with the axillary portion of the chest wall. In between these two extremes all grades can occur. In the extreme cases practically the entire extent of the pleura, both visceral and parietal, is compromised in the infectious process and no further extension can conceivably take place. In the others the differentiation from the cases in the first group is one only of relative size. Here, too, the character of the adhesions present is exactly similar, and, while when the condition is still fresh they may give fairly readily to the finger, as time goes on, they acquire more and more a cartilaginous consistence and the use of scissors and scalpel are required before the parts can be separated.

On a number of occasions while operating upon children and when conditions similar to those described were present, I have purposely broken through the limiting adhesions bluntly with the finger and have liberated the lobes of the lung as far as I could reach. It was easy in the children to reach as high as the apices of the upper lobes and widely from side to side. Comparatively large areas of uninfected and uninvolved portions of the parietal and visceral pleura were bared to the infection; yet the clinical course after operation gave no indication either in temperature, pulse or other objective or subjective symptom that the pathological process had been increased in extent.

3. The third group includes the cases of empyema associated with lung abscess for which radical operations (lobectomy) are done. Under such conditions the actual proof of the spread of intrapleural infection during operation has been given to me on one occasion, but I do not believe this experience to be unique.

This was a man with a pulmonary abscess fairly well localized in the upper right lobe. A lobectomy was done while the rest of the pleura was guarded from infection by appropriate means. At the conclusion of the operation the resultant cavity was lightly packed with iodoform gauze; in addition a counteropening was made into the costophrenic sinus and a tube was led in through this opening and brought up to the level of the uppermost portion of the

thorax near to the stump of the upper lobe. The man died some ten days later. The postmortem examination showed marked infection of the cavity resulting from the extirpation and an abscess between the under surface of the lower lobe and the upper surface of the diaphragm which did not communicate with the drainage tract. The intervening portions of the thorax were apparently clear, though, to be sure, the visceral and parietal pleuræ were adherent throughout with the exception of that part occupied by the tube (drainage tract).\*

Cases of this kind are really primary operative infections of the pleural cavity and resemble very much infection of the peritoneum during a laparotomy with residual abscess formation.

The assumption seems justifiable, therefore, that in the ordinary case of empyema the danger of spreading the infectious process by open thoracotomy is relatively small. In truth the present custom of operating does not permit of any spread of infection. The extent and boundaries of the empyema cavity are accurately delimited prior to operation by adequate roentgen-ray examinations, so that the most favorable point for drainage can be definitely established beforehand. The operation, and this, of course, refers to the early cases and to primary operations carried out at the most opportune time, becomes then merely an incision into an abscess (empyema) cavity and the institution of proper drainage; such a procedure carries a minimum of danger of spreading the infection. In the very exceptional case in which for one or another reason it is deemed advisable at the primary operation to part the adhesions in order to liberate the lobes of the lung, the experience detailed seems to show that little need be feared of the danger of spreading the infectious process to hitherto uninvolved surfaces in all but the lung abscess cases.

Perhaps in some of the cases which have come under my observation some spread of infection has occurred, but having given no perceptible evidence it was unrecognizable in the general clinical picture with the means at our command. Such an occurrence is wholly compatible with the statement made immediately preceding. The character of the infecting organism and the intensity of its virulence as compared with the resisting powers of the patient would have most important bearings on this phase. In several children, in whom the presence of no adhesions and the involvement of the total parietal and visceral surfaces of the pleura indicated that the process most probably followed the rupture of a small superficial focus of liquefaction in a pneumonic lobe, (Rosenbach) a thorough consideration of the history and the clinical course failed to show that any extraordinary symptom had marked the onset of the pleuritis

\* Case from surgical service, Mt. Sinai Hospital.

and its conversion into an empyema. On the other hand the phenomena accompanying the rupture of an acute pulmonary abscess into the pleural space is marked by an extreme increase in the clinical symptoms, and especially in the toxemia. The manifestations of an operative infection of the pleura, as, for instance, that following a lobectomy for a chronic lung abscess, are not so prominent and are probably much mitigated by the immediate institution of ample drainage.

Methods of drainage of the chest, now as formerly, are essentially one of two—intercostal incision\* and rib resection. Intercostal incision is the older operation. Many years ago it was the operation universally employed; but there was much difficulty with the after-treatment, especially from the point of view of securing adequate drainage, and gradually the method was abandoned and replaced by rib resection. In the series which I studied and reported in 1915, 21 of the patients (total number 299) were operated upon by intercostal incision. These were the desperately sick cases, and the operation was done as a matter of expediency rather than as a matter of choice. The important point that was brought out was that there never was any trouble in securing adequate drainage; the healing of the wounds was not only not impeded but actually hastened. Since that time my experiences have only served to substantiate this viewpoint, and I have done intercostal incision practically to the exclusion of other methods. At the present time there seems to be little doubt that from the mechanical point of view intercostal incision and rib resection are equal for drainage purposes, and if intercostal incision is otherwise satisfactory for desperately sick patients, I can see no reason why it should not be equally efficient for the ordinary cases. I have had no cause to regret this attitude, and since the outbreak of the first epidemic of influenza and since the occurrence of the large numbers of pneumonias, with their consequent empyemata, in the various army camps, this opinion seems to be confirmed by the increased favor with which intercostal incision is being regarded throughout the country.

It is difficult to understand why the opinion should have become prevalent that intercostal incision does not yield a drainage equal to that obtained by rib resection. By using one or several appropriately sized tubes and making the incision between the ribs long enough a comparatively large opening is very readily obtained both in children and in adults. As a matter of fact the actual opening

\* Continuous drainage through an intercostal opening made with an ordinary trocar is after all nothing but an intercostal incision. In children and infants it may be all that is needed; in adults the opening obtained is much too small for efficient work especially when one wishes to make use of irrigations with an antiseptic solution. When combined with suction it is, of course, the old Bulau method of treating empyema.

leading into the thorax, when rib resection is done, is very seldom any larger than that obtained with intercostal incision; it is only the outer wound, perhaps, which is larger and that is inconsequential. When the tube, or tubes, are properly placed there are no impedimenta to the outflow of the thoracic contents; drainage is perfect and no retention of pus can be demonstrated. I have frequently seen retention and fever after thoracotomy for empyema, but just as often this was present in cases which had had a rib resection done as in those with intercostal incisions, and I feel quite sure that many other men have had similar experiences.

Except for some special purpose I have abandoned rib resection, and as time goes on the exceptions to the rule and the special reasons are growing less. There are two very valid objections to rib resection as I see the problem since an equally efficient drainage can be accomplished with intercostal incision.

The usual method of doing rib resection is practically an enucleation of a segment of rib from its periosteal covering. When done in that way much newly formed bone is thrown out from the osteogenetic layers, and because the latter lies on the inner side and circumscribes the drainage tract the new bone is crowded in between the adjoining ribs; commonly it becomes superabundant; large plates of bone then form which cause mechanical hindrances to the normal respiratory excursions of the chest wall. The sinus itself becomes surrounded by a bony wall which, more frequently than is apparently recognized, forms an obstacle to the proper closure of the sinus. Both of these form prolific sources for the formation of chronic empyema sinuses and for repeated operations. Both of these undesirable phases can be obviated by excising the rib *in toto* after the suggestion of Lilienthal.

A solution of continuity of the rib opens up surfaces of bone tissue to infecting agencies. In the previous communication (1915) I was under the impression that this was immaterial and that the rib was able to avoid, or quickly overcome, any infectious process to which the environment might lay it open. I have since been disillusioned. Fairly frequently the rib becomes infected, an osteomyelitis affects the rib for a variable distance from the cut surface and healing is prolonged until the dead bone is cast off or until a similar result is obtained by operation. The process may also involve any part of the new bone formation which is thrown out around the drainage tract. When the segment removed is in the immediate neighborhood of the costal cartilages the probabilities are strong that the cartilage, too, will become infected; this would be a rather serious complication. In a communication relating to the infections of the cartilages, Moschcowitz<sup>7</sup> pointed out that an infected cartilage never heals spontaneously, and only heals after operation when every bit of it is removed down to healthy portions of the bone to



which the cartilage is attached. In the connecting segments of the cartilages this would entail an extensive secondary operation before closure of the sinus results.

All of these troubles can be very nearly avoided by making the intercostal incision. Occasionally when a tube too large for the intercostal space is employed, pressure necrosis of the soft parts overlying the rib results in a superficial baring of the bone; the latter does not compare, however, with the osteomyelitic process set up in a resected rib.

A very important advantage of intercostal incision is that the operation can be very easily done in bed. With a very sick and toxic patient, or in one with a badly compromised circulation, the transportation of the patient to and from the operating room is a very serious item. I am quite sure that several of the fatalities which I have seen have been due to this cause. The simplicity of intercostal incision, as compared with rib resection, is extreme.

I believe that it is important not to make the drainage opening in the chest wall of larger caliber than the diameter of the main bronchus entering the lung. Expansion of the lung is a very necessary factor in the contraction of the empyema cavity, and it is only accomplished by the current of air entering and distending the interior of the lung. Ordinarily this has no opposing force. With a fistula in the thoracic wall a current of air is sucked into the empyema cavity with each inspiration, and if its volume is larger than that entering the normal channel, no distention of the lung substance occurs.

The simplest form of drainage apparatus—an ordinary rubber tube—is the best. It is usually taught that it is sufficient for the tube to project just within the inner surface of the thoracic wall in order to obtain complete drainage. Theoretically this should be so; practically it is very frequently not so, especially with the larger cavities, and drainage is not efficient. It is found to be better practice to allow the tube to project into the thorax for a little way and to shorten it progressively as the empyema cavity shows signs of contracting. Various forms of drainage apparatus, with and without valve formations, and manufactured of various materials, have been proposed and employed, and each is said to have some special advantage; but none of these can compete in flexibility of application with the ordinary rubber tube.

In the last two or three years the addition of a suction apparatus in the after-treatment for the purpose of aiding the constant evacuation of the chest has become very popular. The method is a very valuable adjunct to the treatment of empyema. It is most comfortable for the patient; it eliminates many dressings; it reduces the bulk of the dressings to be carried; it permits the collection of the wound discharges in some kind of receptacle and prevents the

maceration of the skin; the pressure in the empyema cavity is more easily kept at a lower level than that in the bronchi and in the interior of the lung and because of this the expiratory effort can more easily help in the contraction and obliteration of the empyema cavity. A disadvantage of the method is that with all the various means of applying suction the patient must necessarily be confined to bed as long as the suction is maintained. A doubtful amount of suction can be maintained by means of a Politzer bag, as in the method described by Bryant. I believe, however, that the method is not very efficient, and after the first few minutes of its application the bag probably exercises none of the function for which it was intended; it is necessary to have the sucking device constantly active to overcome the leakage which occurs around the drainage apparatus.

The antiseptic treatment of empyema wounds has grown very much in favor. The principles and technic, as developed by Carrel and Dakin, are employed for this purpose. It is hoped to secure a complete sterilization of the empyema cavity with the object of secondarily closing the outer wound; the length of time necessary for complete cicatrization of the wound is thus very materially shortened. In actual practice this ideal result is not always accomplished because of the following reasons: in empyema complicated by broncho-pulmonary-cutaneous fistula the method is not applicable; it is very frequently impossible to secure complete sterilization, owing to the difficulties of the technic to be employed; when, apparently, sterilization is secured, closure of the outer wound by suture is not always successful, or a secondary collection of pus having accumulated within the thorax the wound reopens shortly and the entire curriculum must be gone through again.

The difficulties in securing complete sterilization are the real obstacles to the successful employment of an otherwise very valuable method. There are a number of reasons why it is frequently impossible to sterilize the cavity: (1) Very often there are sacculations to the cavity connecting with one another by comparatively small and not easily accessible channels; or there are several independent collections of pus situated at different locations within the thorax; if the antiseptic solution does not reach every part of the interior of the cavity the method is, of course, futile. (2) Small foci of infection can be located in one or many parts of the wall of the empyema cavity, and when liquefaction occurs the pus ruptures into the empyema cavity and reinfects the latter. These foci may be in the superficial parts of the pulmonary parenchyma and result from the original pneumonic condition, or they are in the parietes. The most important of the latter reside in the ends of the resected ribs: I referred above to the disadvantage of rib resection; the parts involved in the osteomyelitic process form a nidus from which the

constant reinfection of the empyema cavity takes place. (3) At any portion of the wall of the cavity the progressive contraction of the latter often lends itself easily, from the formation of superfluous adhesions, to the production of small retention abscesses; sooner or later these rupture and reinfect the original cavity. All of these may lie dormant for relatively long periods of time and I believe that at least some of the "secondary empyemas" which make their appearance after the thoracotomy has apparently healed solidly are due to such causes.

In the instillation of Dakin's solution into the empyema cavity there are wide differences in practice among all of the men especially as to the amount of fluid to be employed. Some use a comparatively small amount—10 to 15 c.c.—others use relatively larger amounts; many use an arbitrarily chosen quantity—usually about 100 c.c.—or the quantity is determined by the length of time the fluid is allowed to run into the chest. Such practice is characterized by a certain timidity and lacks the precision which is a highly desirable factor. Inasmuch as it is very essential to secure an actual contact between antiseptic solution and the entire surface extent of the cavity to be sterilized in order to secure the actual sterilization, it is necessary in some way to employ the method with this object in view. Many employ a number of Carrel instillation tubes, which, being stiffened with wire, are made to reach all surfaces of the cavity; the fluid flowing inward is thus made to reach all surfaces; the amount of solution is, however, comparatively small; the contact of fluid and wall is only present for a few seconds, and thereafter the fluid settles in the bottom of the cavity and a relatively large part of the interior is not in contact with the solution.

I make use of a large tube for drainage, which is coupled with the suction apparatus. The tube leading from the chest to the collecting bottle is made to connect by a T-tube with the reservoir containing the Dakin solution. The total capacity of the empyema cavity is measured with water and noted. The amount of Dakin's solution which is instilled at two-hourly intervals is equal to a few cubic centimeters less than the measured capacity. At the appropriate time the suction is blocked off with a clamp and the Dakin solution is allowed to run in to the amount indicated. Inasmuch as the effect of the free chlorin liberated from the solution is only operative for a very few minutes, there is no necessity for allowing the solution to remain in the chest for any length of time and at the end of fifteen minutes the suction is reestablished and the entire contents are evacuated from the thorax. The suction is allowed to continue until the next instillation. If desirable the procedure can be repeated at hourly, instead of two-hourly, intervals.

It seems to me that this method is most satisfactory for assuring an intimate contact of antiseptic solution and surface to be sterilized.

The large amount of fluid, employed as I have indicated, flows easily into the main cavity; it flows just as easily through any narrow communication into any subsidiary loculi or around any obstructing adhesions; it makes contact efficiently with smooth or distorted or irregular cavity walls and with that of any subsidiary cavities; it remains in contact for the full time for which the fluid is of any use.

The use of any method of irrigation is a new departure from the custom maintained up to the time of publication of the studies of Carrel and Dakin. One has always been taught that irrigation of any kind is dangerous when employed within the chest and from time to time serious consequences have been reported. The knowledge has, perhaps, been a deterrent to the use of Dakin's solution in some quarters and has encouraged the use of small quantities cautiously instilled in others. It is known that similar accidents follow the use of other intrathoracic procedures, especially puncture and aspiration of the chest. There have been no untoward effects or results in my experience with Dakin's solution. I realize, however, that a certain amount of danger exists, but I believe that the method ought to be persisted in because of its intrinsic value, especially since the actual danger of the irrigations is after all relatively and numerically very small.

The presence of a bronchopulmonary fistula of any magnitude makes the method impossible of application, owing to the "gassing" of the patient by the liberated chlorin gas. I remember several patients who showed a moderate amount of distress from this irritation, and if I had followed the usual practice I should have immediately abandoned the irrigations as part of the after-treatment. On subsequently repeating the irrigation I was surprised to note the absence of any irritative signs and thereafter the solution was tolerated very well. I remember in a number of other patients that signs of chlorin irritation were apparent at late periods of the post-operative course which were present on only one, or at most several, occasions in each patient, but which were not sufficient to deter us from continuing the use of Dakin's solution. The probabilities are that minute fistulæ were present which in some way were quickly closed, or which, because of their tortuosity or other mechanical obstruction, did not always permit any of the solution to enter the parenchyma of the lung. Perhaps the irritation of the chlorin was itself effective in closing the fistulæ because of the inflammatory swelling of the tissues making the sinus tract. At any rate if the initial trial of solution is followed by embarrassment the effect ought to be corroborated by a second more carefully carried out instillation before the irrigations are definitely abandoned.

There is a great deal of difficulty in making an accurate determination of the sterility of the cavity. The smear method is not at all reliable, not only because of the possibilities of error while looking

through the smear, but because it is common knowledge that many colonies of bacteria will grow on media when no organisms are visible in the smear. Cultures are always necessary. The sterility of the outer wound is quite easily demonstrated; within the cavity it is not possible to reach all parts for specimens; and while seemingly all that are obtained are sterile, other foci may be present which harbor many organisms. It is quite true that an absolute sterility is not necessary for the secondary closure of the wound.

As soon as the sterility of the cavity is established with a reasonable degree of certainty the practice is to discontinue all forms of irrigation or other treatment. The immediate suture of the outer wound is perhaps not advisable, owing to the frequency with which the wound reopens to permit the discharge of retained pus. It is much better practice instead to simply cover the wound with a dry dressing and to permit the wound to heal by granulation. The outer wound closes very rapidly; a larger or smaller cavity—a pneumothorax—remains which, when truly sterile, does no harm; after a time the pneumothorax becomes absorbed and the cavity becomes obliterated. The pneumothorax shows no clinical evidences either subjectively or objectively. Permanent healing of the cavity must necessarily occur by complete obliteration. This probably occurs as a creeping adhesion of the adjoining parietal and visceral edge of the lining granulation membrane.

In order to obtain good results constant and persevering attention is needed in the postoperative period. The work of the Empyema Commission has shown the importance of maintaining the nourishment of empyema patients at as high a level as possible; special attention is necessary to the nitrogenous elements of the diet. This corresponds with our previous knowledge in regard to the feeding of patients afflicted with suppurating foci. The importance of not neglecting the primary condition to which the empyema is secondary cannot be overemphasized and the rule holds good both with the epidemic and with the ordinary cases. During the postoperative course the primary illness—especially the pneumonia—may continue, or, after it has apparently subsided, it may recrudescence. Other complications are numerous and in children these frequently take the form of intercurrent disease having no or little relation to the thoracic condition. The importance of all of this is readily appreciated when it is known that under ordinary circumstances approximately 20 per cent. of empyema patients die as a result of the primary illness, or of a recurrence of it, or of some other complication or intercurrent disease; under extraordinary conditions (epidemics) the percentage is considerably higher. The table of complications given in my 1915 communication is reproduced for the sake of emphasis.

TABLE OF COMPLICATIONS.

	Cases.	Deaths.
Pneumonia . . . . .	23	19
Pneumonia and pleural effusion . . . . .	2	2
Bronchial fistula . . . . .	4	
Empyema on other side . . . . .	2	2
Pulmonary edema . . . . .	4	4
Bronchiectasis . . . . .	1	
Cellulitis of chest wall . . . . .	2	
Necrosis of resected rib . . . . .	4	
Subcutaneous abscess at a distance from the empyema wound . . . . .	9	
Brain abscess . . . . .	2	2
Bacteremia . . . . .	5	5
Tuberculosis of the resected rib . . . . .	1	
Middle ear suppuration . . . . .	14	2
Thrombosis of lateral sinus . . . . .	1	1
Meningism . . . . .	2	1
Cerebrospinal meningitis . . . . .	1	1
Tuberculous meningitis . . . . .	1	1
Acute endocarditis . . . . .	1	1
Myocarditis . . . . .	1	
Acute insufficiency in chronic valvular disease of the heart . . . . .	1	1
Nephritis . . . . .	4	2
Nephritis, pulmonary edema . . . . .	1	1
Pyelitis . . . . .	1	
Catheter infection in a tabetic . . . . .	1	1
Pharyngeal diphtheria . . . . .	1	
Measles . . . . .	2	
Pertussis . . . . .	1	
Scarlet fever . . . . .	1	
Enterocolitis . . . . .	2	2
Follicular tonsillitis . . . . .	1	
Rickets . . . . .	1	1
Marasmus . . . . .	2	2
Subacromial bursitis . . . . .	1	
Pott's disease of the spine . . . . .	1	
Amyloid disease of the viscera . . . . .	1	
Nevus of vocal chord; asphyxia . . . . .	1	1
Acute mastoiditis . . . . .	1	

The important complications listed by Stone,<sup>7</sup> Bliss,<sup>5</sup> and Phillips<sup>9</sup> (Fort Riley cases) include the following:

Pericarditis . . . . .	5.9 per cent.
Large pleural effusion . . . . .	4.8 "
Substernal pus pockets . . . . .	3.3 "
Pulmonary abscess . . . . .	3.0 "
Peritonitis . . . . .	2.7 "
Endocarditis . . . . .	1.2 "
Miliary tuberculosis . . . . .	0.8 "
Meningitis . . . . .	0.3 "
Pulmonary embolism . . . . .	0.2 "

The important complications listed by Vaughan and Schnabel<sup>10</sup> (Camp Sevier cases) include pericarditis, urticaria, peritonitis and arthritis. Multiple complications were common. The complications noted by Stone, Bliss and Phillips<sup>9</sup> and by Vaughan and Schnabel<sup>10</sup> reflect more especially conditions associated with epidemic conditions.

In the postoperative period fever of one kind or another is a very common phenomenon. Most frequently it is due to any one, or more, of the complicating conditions just enumerated and the explanation of the fever is simple; occasionally the demonstration of the cause is difficult. Very commonly fever is due to the retention of pus within the wound; very commonly the amount of retained pus does not correspond, apparently, with the degree of fever but improvement in the drainage immediately results in the fall of the temperature. The retention of pus is sometimes located within the pulmonary parenchyma either in a definite focus of lung suppuration or within the confines of a bronchopulmonary fistula, from either one of which the escape of the purulent discharge is temporarily impeded.

A moderate grade of fever running along for some time is quite commonly caused by an osteomyelitis of the rib.

Under the newer methods of treatment there has been a pronounced improvement in the results obtained with operations for empyema. Less frequently than heretofore the sinus in the chest fails to close within a reasonable length of time. Difficulties arise with the interpretation of the latter term, for a length of time which is "unreasonable" to one man is regarded with more or less indifference by another. Lilienthal<sup>14</sup> waits only a very short time after doing the primary intercostal incision—minor thoracotomy—before he proceeds to do his larger operation of major thoracotomy; he believes the secondary procedure necessary in a great many of the cases. Recently, Aschner, who is associated with Lilienthal, expressed the opinion\* that the secondary major thoracotomy is not necessary as often as was first believed. My own experience has led me to the opinion that minor thoracotomy is all that is necessary in the very great majority of the patients when none of the impeding factors spoken of below are present. In any case I am accustomed to wait a very long time before doing any secondary operation as long as I am sure that drainage is perfect and that there are no mechanical factors interfering with the cicatrization of the wound. I was very much influenced toward this opinion by the course of the healing of the wound in the following case:

A middle-aged man was operated upon by rib resection for a post-pneumonic empyema; the sinus persisted for fifteen months, at the end of which time I saw the man for the first time. A small opening was present in the chest which discharged some foul pus; the roentgen ray showed a homogeneous shadow covering the whole of the involved side. A radical operation having been determined upon the chest was opened widely through an intercostal space and the incision was prolonged upward, posteriorly, parallel to the spine, with division of the ribs (Torek). An enormous cavity was dis-

\* In a personal communication this opinion was confirmed by Lilienthal.

closed reaching from the very top to the very bottom of the thorax and fully as wide as the depth of the chest. Owing to the presence of a large amount of very foul pus the intention to proceed with an extensive thoracoplasty (Schede) was temporarily abandoned until the suppuration could be controlled. The wound was left wide open and was dressed after the Carrel-Dakin technic. At the end of six months the outer wound had contracted and closed down to a very narrow slit. I had hoped from the way the wound had been healing that any further operation would be unnecessary; but at that time six months seemed "unreasonably" long and I determined to proceed with my original intention. On reopening the wound I was astounded to see that the original huge cavity had contracted down to a narrow gutter barely a finger's breath in width. I am quite sure that if I had waited, but a little while longer, the entire wound would have closed spontaneously.\*

There are a number of factors which interfere with the closure of the thoracic sinus after operations for empyema. Practically all of these functionate by constantly reinfecting the cavity which is to cicatrize, and many of them are those which interfere with the proper sterilization of the wound with Dakin's solution. Over some of these we have almost perfect control, as, for example, a badly carried out drainage or an osteomyelitis of the resected rib. Over others we have only partial control: such would be those empyemata which are not simple cavities but in which the main cavity is complicated by subsidiary loculi; the drainage of the latter is at best imperfect.

The more I see of empyemata the more I am convinced that the greatest obstacle to healing is the presence of a bronchopulmonary fistula: over this impediment we have no control at all. The fistula may be so small as to readily escape demonstration. I feel convinced that bronchopulmonary fistula is a very frequent complication of empyema even in cases in which no disturbance in the healing is apparent and in which, of course, no inkling of its presence can be furnished. This should not appear extraordinary in view of the opinion that many, if not all, of the empyemata complicating pneumonia result from the superficial abscesses (Rosenbach)<sup>13</sup> which rupture into the pleural cavity. The importance of bronchopulmonary fistula in causing chronic sinuses seems to be corroborated by the further observation that almost all of the chronic sinuses follow the postpneumonic type of empyema. My experiences seem increasingly to show that as a cause for chronic empyema sinuses, bronchopulmonary fistula holds first place.

In previous years much has been said about rigid cavities as efficient causes for the failure of closure of the thoracic sinuses. I do not believe, however, that the rigidity of the empyema walls—and

\* Private records.



here, of course, I speak especially of the visceral layer—is a primary phenomenon. I have the impression that it is distinctly a secondary process, owing its presence to any one of the causes mentioned in this communication, which functionate as impedimenta to the healing by constantly reinfecting the cavity. The constant reinfection is conducive to an overproduction of scar tissue in the granulation membrane lining the cavity, and the superabundance, by its very massiveness, lends the unyielding qualities to the visceral surface. A vicious circle is thus formed, so that frequently a pneumolysis of some sort is necessary to permit, or to aid in permitting more rapidly, the expansion of the lung. But in very many cases the efficient removal, operative or otherwise, of the essential primary cause is followed by a progressive yielding of the membrane and an obliteration of the cavity. It is significant that with increased knowledge much less has been said in the last few years of rigid cavities as causes for chronic empyema sinuses.

Recurrences of empyema are fairly common. I should rather term this an incomplete healing of the original empyema. The essential cause for this accident is again an incomplete sterilization, or a reinfection, of the cavity; and the causes for the latter include: (1) Incomplete obliteration of the original cavity; (2) a bronchial fistula; (3) rib sequestra; (4) islands of dormant bacteria in the walls of the empyema cavity; and (5) the retention of foreign bodies.

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14. Lillenthal: Ann. Surg., July, 1919, and September, 1917.

### SUBSTERNAL GOITER, WITH PRESSURE SYMPTOMS.<sup>1</sup>

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**Summary.** Female, aged sixty-four years, suffering from goiter, with symptoms of hyperthyroidism. Enlargement of the thyroid

<sup>1</sup> Read by title at the meeting of the Association of American Physicians, Atlantic City, May 4 and 5, 1920.

gland above the sternum very marked. The tumor also extended below the sternum and by pressure on the right phrenic nerve produced paralysis of the right side of the diaphragm and by pressure on the recurrent laryngeal nerve produced partial paralysis of the right vocal cord; it also displaced the heart toward the right side, producing a loud systolic murmur, with its intensity at the apex and a marked myocardial insufficiency.

**Treatment.** Roentgen ray, rest and medication.

**Result.** A fairly satisfactory recovery, the paralysis of the right diaphragm and right vocal cord remaining.

April 10, 1917. *Personal History.* Thirty-three years ago the thyroid gland began to enlarge and it has been enlarged ever since, but the patient has never had any symptoms referable to this condition. In 1916 I found pus in her urine, which readily yielded to treatment with urotropin, and benzoate of soda. In the winter of 1917 pus was again found in her urine and disappeared under the same treatment.

December 1. The patient's present illness began during the summer of 1917, while at her summer home at the seashore. During August of this year she suffered from mental depression and shortness of breath. Early in September she consulted a physician, who found that she had a well-marked cardiac murmur and that her urine contained pus.

About the middle of October she was taken to New York and placed under the care of a physician, where she remained until her return to Cincinnati on November 29, 1917. Her physician in New York reported that she had dyspnea on exertion, a well-marked systolic heart murmur, a blood-pressure of 148-74, a sterile blood culture and a negative Wassermann. On October 22 a blood examination showed hemoglobin 85 per cent. red blood cells 5,400,000, white blood cells 5000, polymorphonuclears 41, lymphocytes 54, eosinophiles 5. The urine examined on October 22 and November 12 contained no pus, and except for a very faint trace of albumin was negative. The patient was kept off her feet and in bed the greater part of the time she was in New York, and during this time she improved very materially. The cardiac dulness decreased.

On sending the patient to Cincinnati her physician wrote: "I feel that Mrs. Blank has for a basis of her cardiac changes a mild hyperthyroidism. She has had from time to time, in addition to the goiter, the following clinical evidence to substantiate this view: (1) Instability of pulse and a marked tendency to develop tachycardia; (2) flushing; (3) tremors."

November 30 I saw the patient at her home, twenty-four hours after her arrival from New York. She had been in bed during that time; she had symptoms of mild hyperthyroidism, a loud systolic murmur was heard most distinctly near the apex of the heart, which was transmitted into the axillary region, and was also heard very

distinctly in the direction of the sternum, extending quite far up along the sternal line over the arch of the aorta. No diastolic murmur was heard. There was a dull area beneath the manubrium continuous with the cardiac dulness; the latter was increased downward and outward.

The left lung appeared normal but the lower border of the right lung upon percussion and auscultation did not appear to extend below the 7th or 8th rib posteriorly and the 4th rib anteriorly. Vocal resonance and fremitus were diminished or absent over the lower portion of the right chest. The vesicular sounds over the whole right lung were less distinct than over the left.

December 6, Dr. Samuel Iglauer, in consultation, found the left vocal cord paralyzed, and the inference was that this paralysis was produced by pressure from some substernal growth or from an aneurysm of the aorta.

A roentgen-ray examination made at this time was as follows: The stereoscopic roentgen-ray plates of the chest showed an opaque shadow beginning just above the arch of the aorta, extending up into the neck, where it became lost in the shadows of the deeper structures. This shadow extended about two inches to both sides of the sternal line. The arch of the aorta on its curve on the left side showed a number of dense shadows simulating calcareous deposits. The lower right side of the chest was opaque. The opacity extended posteriorly from below upward as high as the 8th rib and anteriorly as high as the 4th rib. The line of this shadow was straight and was evidently the lower border of the diaphragm. The fluoroscopic examination showed the same shadow in the same position, with no apparent movement of the diaphragm on the right side. The heart shadow appeared normal in size and pushed slightly to the left.

The roentgen-ray films of the teeth showed no root abscesses.

A blood examination showed hemoglobin 85 per cent., red blood cells 5,000,000, white blood cells 5200, lymphocytes 37 per cent., large mononuclear leukocytes 7.66 per cent., polymorphonuclear neutrophils 52.66 per cent., eosinophiles 1.3 per cent., mast cells 1 per cent., myelocytes 0.0, Tuerck's irritation forms 0.3 per cent.

At this time, in addition to the diagnosis of enlarged thyroid with hyperthyroidism, it was our belief that that portion of the enlarged thyroid gland extending beneath the sternum pressed upon the recurrent laryngeal nerve, producing paralysis of the vocal cord, and also pressed upon the right phrenic nerve, producing paralysis of the diaphragm.

This patient was seen in consultation by Dr. Roger Morris and Dr. Max Dreyfoos on December 17, and on January 26, 1918. She was also seen on January 28, 1918, by Dr. James B. Herrick, of Chicago.

The physical findings and diagnosis as above recorded were con-

firmed by the consultants, and it was decided to seek surgical advice with reference to the advisability of a surgical operation.

It was the opinion of myself and all the medical men who had studied this case that it was not advisable to attempt the removal of the substernal thyroid, which was producing the pressure symptoms.

During the last week of February, 1918, the patient was taken to Chicago for medical and surgical advice. She returned to Cincinnati in about ten days, with medical and surgical opinions that it was not advisable to attempt an operation, and also with the advice that the medical treatment which she had had before going to Chicago should be continued.

At this time the prognosis was considered very bad by all the physicians and surgeons who had seen her. On her return to Cincinnati the treatment which she had received from the time she came under my observation was continued, and the remarkable improvement in her physical condition which has resulted I think justifies the clinical report here given.

**Treatment.** On December 1, 1917, when the patient first came under my observation, she was given 15 drops of tincture of digitalis three times a day. From that date to the present, covering a period of two years and four months, she has continued to take digitalis, omitting it for only short periods of time. At the present time she is taking 5 drops of the tincture twice a day, six days in the week. The dose has been gradually diminished and has been omitted occasionally for short periods. During nearly all of this time she has taken a capsule containing  $2\frac{1}{2}$  grains of the neutral bromide of quinin, 1 grain of extract of ergot and  $\frac{1}{30}$  grain of extract of belladonna.<sup>2</sup> This capsule was given three times a day for a long period of time, and throughout the two years and four months it has been taken almost continuously. During the past year she has taken two of these capsules per day. At rare intervals this treatment has been interrupted for a period of a few weeks.

In addition to the above treatment the patient took deep roentgen-ray treatments over the thyroid gland, given from two areas in the front and two in the back, never giving more than two areas at one time. These treatments, fifteen in all, were given by Dr. William M. Doughty on the following dates:

1918—January 4 and 15; March 5, 15 and 29; April 12 and 26; May 17; June 8; November 8; December 2.

1919—January 7; April 15; May 20; June 9.

These treatments were all filtered through 4 mm. of aluminum.

When the patient came under my observation, December 1, 1917, she was practically confined to her room, spending most of the time in bed or upon a couch. Even the slight exertion of walking about

<sup>2</sup> The above prescription was a favorite one of the late Dr. Frederick Forchheimer, of Cincinnati.

the room produced shortness of breath and increased rapidity of heart action. During this time she was occasionally carried up and down stairs, and some months later was strong enough to take automobile drives. After four or five months of treatment her heart had sufficiently recovered for her to walk up and down stairs once a day. She has steadily improved in strength, so that at the present time she leads practically a normal life and presents the appearance of being in perfect health.

The physical signs so far as the lungs are concerned persist. The right diaphragm is in the same position as above described. An examination of the heart still shows a systolic murmur, which is loudest at the apex. This murmur, however, is now soft and very much diminished in intensity, and in the range of its transmission. It is my belief that at the present time the shortness of breath, still experienced after taking long walks, is due rather to the diminished lung capacity of the right lung than to any cardiac weakness.

The patient has not had a roentgen-ray treatment for nearly a year, and for more than a year there has not been any evidence of hyperthyroidism.

## REPORT OF A CASE SHOWING THE RELATION BETWEEN OCCUPATION AND A CERTAIN CASE OF BRONCHIAL ASTHMA.

BY JACOB ROSENBLOOM, M.D., PH.D.,

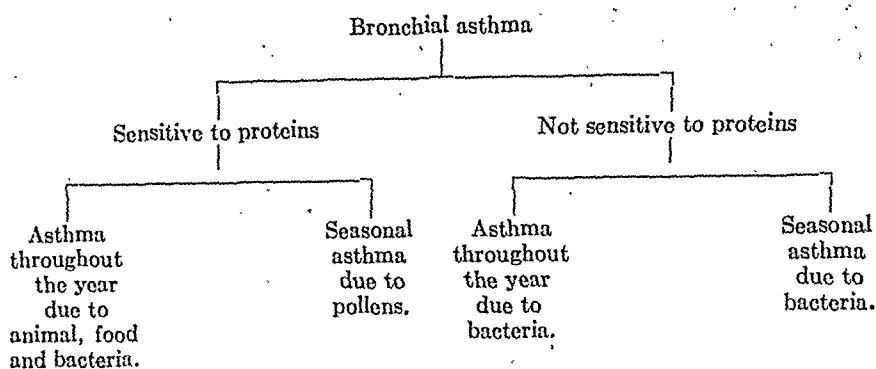
NEW YORK CITY.

It will be recalled that our present conception of bronchial asthma differs greatly from that previously held. We now know that by means of the cutaneous or skin test cases of bronchial asthma that are sensitive<sup>1</sup> to proteins may be separated from the non-sensitive type. The first class, or true bronchial asthma, is separate and distinct from the second, non-sensitive type, the so-called asthmatic bronchitis.

The following classification of Walker<sup>2</sup> presents this in an interesting way:

<sup>1</sup> For studies showing possible relationship of bronchial asthma to anaphylaxis and to the amines see: Friedberger and Moreschi: *Berl. klin. Wchnschr.*, 1912, xlix, 741. Oehme: *Arch. Pharm.*, 1913, lxxii, 76. Baehr and Pick: *Arch. f. exper. Path. u. Pharm.*, 1913, lxxiv, 41, 65. Meltzer: *Jour. Am. Med. Assn.*, 1910, lv, 1021; *Tr. Assn. Am. Phys.*, 1910, xxv, 66. Eustis: *Am. Jour. Med. Sc.*, 1912, cxliii, 862; *New Orleans Med. and Surg. Jour.*, 1914, lxvi, 730; 1909, lxi, 98. Eppinger and Gutman: *Ztschr. f. klin. Med.*, 1913, lxxviii, 411. Dale and Laidlaw: *Jour. Physiol.*, 1910, xli, 318; 1911, xliii, 182. Pfeiffer: *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 1911, xi, 133. Biedl and Kraus: *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 1912, xv, 447. Schittenhelm and Weichard: *München. med. Wchnschr.*, 1912, lix, 67. Aronson: *Berl. klin. Wchnschr.*, 1912, xlix, 642.

<sup>2</sup> *Bronchial Asthma, The Oxford Medicine*, 1919, ii, 128.



The following are the essential points, in the history of the case of true or sensitive bronchial asthma, that I wish to report.

Mr. Z., aged forty-four years, a baker for twenty-six years, has suffered continually from chronic bronchial asthma for a period of fourteen years. About every second or fourth week he develops an acute attack. The physical examination shows some emphysema, otherwise it is negative. Laboratory examination of the urine, blood and feces reveal nothing of importance.

The patient was tested with the following proteins:

Almond	Egg, whole	Perch
Asparagus	Egg yolk	Pike
Banana	Fig	Pineapple
Barley	Ginger	Plum
Bean	Goat meat	Pork
Beef	Goose	Potato
Beet	Grapefruit	Radish
Blackberry	Guinea-hen	Raspberry
Bluefish	Haddock	Rhubarb
Brazil nut	Herring	Rice
Buckwheat	Lactalbumin	Rye
Cabbage	Lamb	Salmon
Cantaloupe	Lentil	Sole
Carrot	Lettuce	Spinach
Casein	Lima bean	Squab
Cauliflower	Lobster	Squash
Celery	Mackerel	Strawberry
Cheese	Milk (breast)	Sweet potato
Chestnut	Milk (cow)	Tea
Chicken	Milk (goat)	Tomato
Clam	Mustard	Turnip
Cocoa	Oat	Turkey
Codfish	Onion	Veal
Coffee	Orange	Walnut (English)
Corn	Oyster	Wheat (whole)
Crab	Parsnip	Wheat gliadin
Cucumber	Pea	Wheat globulin
Duck	Peach	Wheat glutenin
Egg-plant	Peanut	Wheat proteose
Egg-white	Pear	Wheat leucosin
	Pecan	
Beef serum	Chicken feathers	Mouse hair
Horse serum	Dog hair	Rabbit hair
Tobacco	Goose feathers	Sheep wool
Cat hair	Horse dander	

Staphylococcus pyogenes aureus  
 Staphylococcus pyogenes albus  
 Staphylococcus pyogenes citreus  
 Micrococcus tetragenus  
 Micrococcus catarrhalis

Streptococcus pyogenes 3-valent  
 Streptococcus pyogenes viridans  
 Streptococcus pyogenes hemolyticus  
 Streptococcus alpha hemolyticus  
 Pneumotoccus 4-valent  
 Diphtheroid

On carrying out the cutaneous tests it was found that the only proteins he was sensitive to were *rye* and *wheat* and *wheat globulin*. Wheat leukosin, wheat proteose, wheat glutenin and wheat gliadin were all negative. The interesting fact is shown that this person is sensitive only to proteins of the rye and to wheat globulin, the other proteins of wheat not causing any reaction. We therefore have a case of a baker sensitive to the proteins of rye and wheat, proteins with which one may say he spends a great deal of time.

Cases showing the relation between occupation and bronchial asthma are not common. The following quotation from Walker<sup>3</sup> is of interest in this connection:

"Occupation may have a direct bearing on the cause of bronchial asthma, and occupation frequently explains the development of sensitization after the age of forty. This occurrence, however, is not usual. Of 11 patients who became sensitive to proteins after the age of forty, 4 were bakers and sensitive to wheat protein, 1 was a hostler and sensitive to horse dandruff protein and 1 was a sifter of green coffee beans and was sensitive to green coffee protein, therefore in over half of these cases occupation was responsible for the cause of the asthma. Three unusual instances where occupation bore a direct relationship to the cause of the asthma are sufficiently interesting to mention. A man whose work consisted of sifting green coffee beans became sensitized to the proteins in the green husks and had asthma from the protein. Another man whose work was that of a jewel polisher became sensitive to the proteins in the dust from boxwood with which he polished the jewels, and a second man, working in the same room, became sensitive to the dust from the orangewood with which he polished jewels. The man sensitized to the boxwood was not sensitive to the orangewood, and *vice versa*."

As regards the treatment of these cases one can proceed in anyone of three ways: (1) The offending protein must be eliminated, that is, it must not be taken in the diet and the occupation must be changed so that the offending protein will not be inhaled. (2) If the protein is only offending on account of the ingestion of the same it can still be taken in the diet, but it must be only used after it has been subjected to a high heat. For example, it is known that patients who are sensitive to potato protein are usually able to eat baked potato, although boiled potato causes symptoms. Raw milk may cause symptoms in patients sensitive to milk protein, but boiled milk will not. Shredded-wheat biscuits and thin slices of bread well toasted on both sides may be eaten by patients sensitive to wheat protein, while the unheated wheat preparation would cause symptoms of ingestion. The explanation for these facts must be that the high temperature that the foods are subjected to destroys the anaphylactic properties of the protein contained in the same.

<sup>3</sup> Bronchial Asthma, *The Oxford Medicine*, 1919, ii, 128.

(3) Consists in treating or desensitizing the patient with those proteins that he has been found to be sensitive to by the skin or cutaneous test. One can give subcutaneous injections of the offending protein, but the procedure is difficult and not as satisfactory as the method of feeding the proteins. In this method gradually increasing doses of the offending proteins are fed until large amounts are taken without the production of symptoms. By this method of desensitization, Schofield,<sup>4</sup> Rich,<sup>5</sup> Schloss,<sup>6</sup> Talbot,<sup>7</sup> and Grover<sup>8</sup> have had successful results in children. Walker<sup>9</sup> states that he has tried this method of treatment with adults, but none have been conscientious enough to take the protein per schedule for any length of time.

## EXPERIMENTAL CHRONIC SUPPURATIVE ARTHRITIS.

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ARTHRITIS has been a subject for experimentation over a period of years, and during this time the effect on the joints by many organisms has been studied. The green streptococci have probably been most extensively used, and have produced the most interesting findings, with not only local joint changes, but, in addition, alterations in the heart, arteries and kidneys, constituting a combination of lesions which simulated not a little those observed in the complex known as acute rheumatic fever.

The character of the joint reaction caused by the *Streptococcus viridans* is of a comparatively mild type, subsiding usually in a relatively short space of time, with a variable grade of disability of the joint. Of the other organisms, the one that bears the most interest is the hemolytic streptococcus, and I wish here to describe some observations made on rabbits treated with a member of this group.

The single strain of streptococcus used in these experiments was isolated on January 8, 1919, from the pus of an abscess in the submaxillary gland in a psychopathic patient who died eight days later of pneumonia. Permission for an autopsy was not granted. It may be stated, however, that during life the patient presented no evidence of bone or joint involvement. The organism in question was

<sup>4</sup> *Lancet*, 1908, i, 716.

<sup>5</sup> *Jour. Michigan State Med. Soc.*, 1914, xiii, 649.

<sup>6</sup> *Am. Jour. Dis. Children*, 1912, iii, 341.

<sup>7</sup> *Boston Med. and Surg. Jour.*, 1916, clxxv, 191.

<sup>8</sup> Reported by Walker (loc. cit.).

<sup>9</sup> Loc. cit.



a Gram-positive coccus arranged mostly in chains of five or six, but at times with as many as ten cocci in a chain. There was no tendency to an arrangement of the cocci in pairs within the chains. On blood-agar it grew in a small, shiny, nipple-like colony, with a distinct, clear zone of hemolysis. Fermentation of lactose and salicin with negative results on mannite and inulin, placed the organism in the class of the common *Streptococcus pyogenes* (Holman). With a streptococcus at hand which had caused a local submaxillary abscess in a human, and showing relatively low virulence, it was deemed a favorable opportunity to study the effect of this organism on rabbits. With the aim in view of preserving a possible elective affinity for the submaxillary gland the organism was cultured in columns of dextrose infusion broth 11 cm. high, and after forty-eight hours the organisms were removed by centrifugation and diluted so that each cubic centimeter represented 15 c.c. of the original culture. Of the thirty-four animals injected with this organism the following doses were given: 1 c.c. to two animals, 1.5 c.c. to 11 animals, 2 c.c. to 19 animals, and 2.5 c.c. to two animals; 26 animals received one injection and 4 each were given two and three doses respectively; 14 of these animals were injected with the original strain, 6 shortly after the organism was isolated and 8 after the organism had been kept three months upon culture media; 20 rabbits were treated with the organism after one animal passage, 13 from one animal and 7 from another. The symptoms presented by the animals following these doses were comparatively mild. Marked disturbances in the general physical condition of the animals were not observed and it was only after a period of several days or at times of several weeks before they showed any discomfort, and this was due to difficulty in locomotion brought about by joint involvement. The length of time that the animals lived following the treatment varied widely, ranging from three to eighty-seven days. One rabbit died on the third day, two on the fourth, five on the sixth, one on the seventh, four on the eighth, one on the ninth, three on the tenth, two on the twelfth, one on the fourteenth, one on the seventeenth, one on the twentieth, one on the twenty-first, one on the twenty-third, two on the thirty-third, one on the thirty-eighth, one on the forty-sixth, one on the sixtieth, and one on the eighty-seventh day. Four animals were killed respectively on the eighth, twenty-ninth, forty-seventh, and sixty-second day. The animals killed on the eighth and twenty-ninth days had been injected with the original strain, while those killed on the forty-seventh and sixty-second had been treated with the organism after one animal passage. The average number of lesions in six animals treated with the original organism was four while that in eight animals treated with the original organism after three months' artificial cultivation was eight. Six animals not included in this list are still living, four apparently well and the remaining two have joint involvement.

Of the first four, two received doses of the organism after one animal passage, while the other two received doses of the organism after three months' artificial cultivation. The remaining two of the six animals have enlarged joints. One of these animals was first injected on January 13 with 1.5 c.c. of the original organism and subsequently was given three doses, the last on April 8, 1919. The only joint enlargement that this animal showed occurred in the left ankle which was three times the size of the right, forming a large spindle-shaped, yellowish red swelling over which the hair was lost. At the present time the ankle has become considerable reduced in size and presents a rather firm, nodular outline. On March 7, the other rabbit was given 1.5 c.c. of the organism after one animal passage. This animal became quite sick and on April 8, showed a left elbow about three times the size of the right elbow and a marble-sized, yellowish red swelling behind both ankles. The hair was absent over all of these joints. At the present time these joints are still enlarged but, somewhat smaller than on April 8. They are boggy and show a yellowish red discoloration through the skin which is now slightly wrinkled over the joints. These animals recovered spontaneously without permanent joint injury.

The lesions produced by the injection of this streptococcus were almost entirely limited to the joints which, in order of frequency, were ankles<sup>1</sup> (21-22), fore-paws (19-16), wrists (16-16), knees (17-15), hind feet (18-13), elbows (10-8), shoulders (6-4), hips (left-1). An exudative lesion was found in the muscles of the leg thirteen times, in the forelegs nine, in the thigh and hip five, and in the back nine. A purulent reaction involving the epiphyseal cartilage of the head of the humerus was noted in two rabbits and a similar change was found at the junction of the ribs and costal cartilage in three animals. The kindeys, peritoneum, pericardium, and pleura were involved once in each instance, while the heart showed myocardial reaction in each of three rabbits without, however, visible changes in the valves.

The joint reaction consisted of a suppurative process characterized by more or less distention of the capsule with a creamy sticky fluid. In many instances there was an extension of the pus into the peri-articular tissues and frequently pus could be traced from one joint to another along the tendons and fascial planes with at times a suppurative involvement of the adjacent muscles. This reaction was noted in the case of the ankles and knee-joints and the wrists and elbows with also the pus following the tendons from the wrists and ankles respectively into the forepaws and feet. Again hemorrhage occasionally occurred into the subcutaneous tissue and muscles of the involved legs and a diffuse, jelly-like, subcutaneous serous exudate was not infrequently observed.

<sup>1</sup> The numbers in brackets after ankles, forepaws, wrists, etc., refer to left and right members respectively.

Smears from the pus in these joints showed many Gram-positive cocci in pairs and short chains with disintegrating endothelial cells and polynuclear leukocytes. However, in many smears no intact cells were observed but rather fragments of nuclei and finely granular debris. The organism injected was recovered in all instances from the joint exudate.

On gross examination the heart and kidney were found to be affected in but three of the animals. However, microscopical study of these tissues showed seven additional animals to have metastatic foci in the heart and kidney. The lesions in all ten of these animals were similar, consisting of areas of necrotic debris surrounded by large and small mononuclear leukocytes. These lesions were of the nature of chronic lesions rather than rapidly advancing abscesses seen in streptococcus infections. In the heart, calcified muscle fibers were seen in several instances with but slight evidence of inflammation. The areas in the heart muscle were commonly found well within the structure and had no particular relation to the endocardium or pericardium. In the kidney the lesions occurred, for the most part, in the medulla and involved the vessels coursing up in the columns of Bertini. They were similar to those observed in the heart with the exception that endothelial cells were more abundant. Embolic glomerular nephritis was not observed, although in several kidneys emboli of cocci were noted in the glomeruli without evidence of inflammation or hemorrhage. The lesions observed in the skeletal muscle were similar to those observed in the heart and kidney.

The literature dealing with the production of arthritis is copious and it is so well known that it is deemed inadvisable to review it at length. However, there are certain facts concerning the localization of organisms in joints that bear especial interest. We are particularly concerned with the peculiar predilection which this streptococcus exhibited for joints. In another paper we called attention to the frequency with which hemolytic streptococci could be isolated from the joints of animals which had been treated with such organisms. Usually hemolytic streptococci are so virulent that they rapidly produce a fatal septicemia which is not characterized by the focal lesions observed in more chronic infections but also in spontaneous human infections with the same organisms. The condition found is one usually associated with extensive hemorrhages. In such states even where there is no gross enlargement of the joints it is found that streptococci can be isolated in a large percentage of cases. Following the experimental administration of streptococci, all grades of inflammation may be seen from the initial congestion of the synovial membrane to the accumulation of the purulent exudate within the sac. The development of the purulent arthritis depends, however, upon the factors which determine the course of infections in general. The physical condition of the animals is very important and it is well known that animals in

apparently similar physical condition frequently react differently to the same organism administered under identical experimental conditions. If the dosage of an active organism is too large the protective mechanism of the body may not accomplish the destruction of the organism and as Bull has pointed out a fatal septicemia may develop. However, if the protective mechanism is competent to efficiently combat the progressive invasion of the offending organism, focal lesions only may develop particularly in the muscle where they grow and may later again be washed into the circulation.

Such focal lesions may arise in many locations although they are found more frequently in the heart, kidneys, joints, and muscles. At times the lesions in one of the above are more important than the others although all are involved in an appreciable percentage of instances.

Thus it would be difficult to ascribe to an organism a particular affinity for a given tissue unless the reaction is read in terms of intensity over and above that noted in other tissues. However, we do find evidence that certain organisms attack tissues with an apparent predilection as has been well demonstrated by Dick in his work on *B. mucosus* arthritis. Characters of this type remain permanent features of an organism and must not be confused with a degree of intensity of reaction which may appear as an elective affinity according to Rosenow.

It has been found possible to produce arthritis in sensitive joints. Within recent years, Herry and later Faber used the toxins of the streptococcus to sensitize the joint. Upon the injection of the streptococcus intravenously at a subsequent period, a definite arthritis was produced. In several animals that had recovered spontaneously from arthritis, Cole was able to provoke a relapse by another intravenous injection of the same streptococcus.

The streptococcus which we have isolated from an abscess of the submaxillary gland presented the unique feature of mainly attacking the joints of rabbits. It was found unnecessary to sensitize the joints and in most instances but a single dose was given to an animal. Further the animals remained in good physical condition and only experienced discomfort from the joint lesions. There was none of the emaciation which commonly occurs early in streptococcus treated animals and most of the animals survived the treatment for a variable number of days. It was only after the development of a well defined arthritis that the organisms again reappeared in the blood in sufficient numbers to cause death. The results obtained in the animals treated with this streptococcus are somewhat different from the picture usually seen in experimental streptococcus infections. In a previous article we recorded the results obtained from injecting rabbits with hemolytic streptococci. Twenty-five of fifty-eight animals gave positive postmortem cultures from the knee-joints but in no case was there a true suppurative arthritis. This

no doubt, was due to the virulence of the streptococci used, as most of the animals died within a period of a few days following the treatment. It may also be indicated that the striking feature in these animals was not the joint involvement but rather a picture of severe infection characterized by extensive hemorrhages.

At the time when the experiments were being conducted with the streptococcus from the submaxillary gland, twenty-five rabbits were used for controls. Fifteen rabbits were treated with hemolytic streptococci from pleural fluid. Five rabbits each were treated respectively with two strains of *S. pyogenes* and five rabbits received injections of a *S. subacidus*. Ten other rabbits were inoculated in series of five with two strains of *S. pyogenes* that were isolated respectively from a herniotomy wound and peritoneal exudate. The results obtained in these animals were in marked contrast to those animals inoculated with the streptococcus from the submaxillary gland in that they presented a hemorrhagic type of reaction similar to that which we had previously reported. These animals were from our own stock and apparently in identical physical condition. The doses administered to these animals were not excessive in that 1.5 c.c. were given to twenty rabbits and 2 c.c. to five rabbits. From these results it would appear that the qualities of this particular streptococcus are somewhat different from others which we have studied. It is difficult to understand why a streptococcus isolated from a human submaxillary gland should have a predilection for the joints of rabbits. It would seem that although this streptococcus showed a remarkable constancy in location and type of lesion produced, the location of the lesions in the animal had no relation to the origin of the organism or to the lesion produced by it in the patient from which the strain was obtained. Results of this kind limit the usefulness of experimental bacteriology for determining a possible tissue predilection for organisms of human origin.

**Conclusions.** From our study of this organism it would appear that we have a streptococcus of fairly low pathogenicity but of rather high invasive quality, which possesses the ability to attack the joints of rabbits and produce in them a chronic suppurative arthritis. This quality of attacking the joints was not lost after a period of three months' artificial cultivation. Although joints were mainly attacked, certain other tissues were involved an appreciable number of times. The organism was of human source, isolated from the submaxillary gland.

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## BLOOD CHOLESTEROL IN GASTRO-ENTEROLOGIC CASES.<sup>1</sup>

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(From the Laboratory of Dr. Joseph Sailer, Philadelphia.)

CHOLESTEROL or cholesterin, a monatomic alcohol, is found as such in the human blood stream. In combination with fatty acids it forms, among other esters, cholesterol palmitate and cholesterol oleate. A fairly definite relation or balance is maintained between the free and combined cholesterol of the blood. Cholesterin is also found in the nervous system, bile, milk and other body tissues and fluids. There is some uncertainty as to the exact chemical structure of cholesterol.<sup>2</sup> It is soluble in ether, chloroform, benzene, fats and hot alcohol.

The origin of cholesterol is, for the most part, exogenous, although there is some evidence that it may have an endogenous source.<sup>3</sup> It is readily absorbed from the intestinal tract contents through the chyle and may be recognized free or esterized in the contents of the thoracic duct.<sup>4</sup> The blood cholesterol content can be readily increased by feeding foods rich in this substance. That the biliary cholesterol can be increased in like manner remains uncertain. Feeding experiments leave this point in doubt. The origin of biliary cholesterol is perhaps to be found in the disintegrating blood cells of the body. Bile is the only suitable solvent in the body for cholesterol, but whether the bile is a normal mode of excretion for this substance is just as uncertain as other facts pertaining to this alcohol. Fistula bile is poorer in cholesterol than gall-bladder bile, and some, therefore, believe that this substance somehow or other has its origin in the lining membrane of this organ. Some contend that this difference in the bile from these two sources soon ends after the unusual conditions imposed by the operation cease;<sup>5</sup> recently, Rous and McMaster<sup>6</sup> seem to have demonstrated an ability on the part

<sup>1</sup> Read before the American Gastro-enterological Association, May 3, 1920.

<sup>2</sup> Hawk: Practical Physiological Chemistry, 5th edition, p. 355.

<sup>3</sup> Klein: Biochem. Zeit., 1910, xxx, 465.

<sup>4</sup> Mueller: Jour. Biol. Chem., 1910, xxii, 1.

<sup>5</sup> Rothschild and Wilensky: AM. JOUR. MED. SC., vol. clvi, p. 2.

<sup>6</sup> Proc. Assn. Am. Phys., 1920.

of the gall-bladder to withdraw normal salt solution from the hepatic bile and thereby concentrate the latter fluid. There is no reason to believe that cholesterol is changed to cholic acid, a substance participating in the formation of bile salts. The liver probably is the regulator of cholesterol metabolism and maintains the level by excretion through the bile.<sup>7</sup>

Both lecithin and cholesterol assume some role in the transportation and metabolism of fats. The esters of cholesterol are found in the red cells and are practically absent during fasting. The presence of this substance in the red cells probably accounts for the role the latter play in fat metabolism.

The amount of cholesterol normally found in the blood has been variously stated. Bacmeister and Havers<sup>8</sup> give 110 to 180 mg. per 100 c.c. and Widal, Weill and Laudat<sup>9</sup> 174 to 195 mg. per 100 c.c. Bloor<sup>10</sup> found the average value for men to be 210 mg. and 230 mg. for women. A wide variety of normals are given by other workers. It is probably fair to say, however, that an upper normal is about 200 mg. per 100 c.c. of blood while the lower level is about 150 mg.

The literature is in accord on the findings of a low blood cholesterol in pernicious anemia which probably has its basis in the diminution of the corpuscular elements to be found in this disease. To beriberi, syphilis, prostration, cachexia and fever are accredited low cholesterol findings, and recently a low blood cholesterol<sup>11</sup> has been found to be of bad prognostic import in nephritis. In non-grave nephritis, arteriosclerosis, obstructive jaundice, diabetes and pregnancy high figures are said to prevail. The literature is by no means in accord as to the constancy of blood cholesterol content in these conditions, and of no disease is this truer than of cholelithiasis. There are those who publish almost constant hypercholesterinemic figures<sup>12</sup> for this disease, while others have had very irregular results.<sup>13 14</sup>

In the winter of 1916-1917, hoping that a determination of the cholesterol content in the blood of gastro-enterological patients would help in diagnosis, especially when the biliary system seemed to be in question, it was planned to examine a series of cases in this way. The Bloor<sup>15</sup> method was employed. Whole blood was used and it was obtained during the morning hours. After a prolonged interruption in the work the number of patients so investigated reached sixty and the number of blood cholesterol readings seventy-five in these cases.

In this group two cases of diabetes showed 160 and 151 mg. from

<sup>7</sup> Rothschild: Proc. New York Path. Soc., December, 1914, N. S., xiv, 229.

<sup>8</sup> Deutsch. med. Wehnschr., 1914, p. 8.

<sup>9</sup> Soc. Biol., 1911, lxiv, 883.

<sup>10</sup> Jour. Biol. Chem., 1916, xxv, 577.

<sup>11</sup> Henes: Arch. Int. Med., April, 1920, xxv, 4.

<sup>12</sup> Henes: Jour. Am. Med. Assn., 1914, lxiii, 146.

<sup>13</sup> Gorham and Meyers: Arch. Int. Med., October, 1917, xx, 4.

<sup>14</sup> Denis: Jour. Biol. Chem., 1917, xxix, 93.

<sup>15</sup> Jour. Biol. Chem., 1916, xxiv, 229.

100 c.c. of blood, while a third case yielded values of 241 and 304 mg. The latter case has a gall-stone history and corresponds in type, but the presence of calculi has never been established. These cases exhibited no acidosis.

Two cases of pernicious anemia showed 139 and 105 mg. Both of these cases presented an achylia gastrica, and it must be assumed that the upper abdominal symptoms here in all probability were gastric in origin. The well-known antihemolytic powers of cholesterol are to be considered in connection with the anemias, and these low figures are interesting in this light. Surroeo<sup>16</sup> contends that cholesterol findings in the blood are a measure of the state of the organic defences, and he is not alone in this opinion. Findings below 129 mg. show a weakness in this respect according to this Frenchman and findings above 200 mg. indicate a slow infection of some type. Findings below 100 mg. are of bad prognostic character.

Assuming that the leukocyte count is a measure of organic defence or an index to the presence or absence of infection we found that the low leukocyte count cases in our series averaged 202 mg. of cholesterol while the increased leukocyte cases yielded an average of 220 mg. A case with only a transient gastro-intestinal upset gave findings of 363 mg. and 336 mg. of cholesterol and had but 5000 leukocytes. Our lowest cholesterol finding was in a case with 100 mg., and white cell counts of 9100 and 10,000. None of our low cholesterol cases appeared to be in grave danger nor to be lacking in defence reactions.

Carcinoma and cholesterol, according to some, present an interesting relationship. Luden<sup>17</sup> reports a high cholesterol content in carcinoma and that cholesterol promotes cell multiplication, especially cells of the malignant variety. Our two cases of carcinoma showed readings of 120 and 180 mg.

Four jaundice cases were of the catarrhal variety and yielded 144, 143, 214 and 171 mg., while a single obstruction case showed 330 mg. This accords with the findings of Rothschild and Felsen,<sup>18</sup> who report high findings in the obstructive jaundices.

In gastroduodenal ulcer our findings were 166, 169, 176, 115 and 250 mg. per 100 c.c. of blood. In three of these cases the diagnosis was made clinically while in one the lesion was found at operation and the other showed a filling defect on roentgen-ray examination.

Intestinal stasis cases apparently uncomplicated yielded the following findings: 279, 172, 136, 125, 108, 180, 480 and 125 mg. per 125 mg. per 100 c.c. of blood. In one case three observations were made of 185, 196 and 240 mg.

In this group of 60 cases, 36 were constipated and addicted to the cathartic habit. Their average cholesterol reading was 226 mg. The highest figure was 440 mg. and the lowest one 100 mg. Those

<sup>16</sup> Ann. de la Fac. de Méd., Montevideo, December, 1917.

<sup>17</sup> Jour. Lab. and Clin. Med., December, 1917, p. 3.

<sup>18</sup> Arch. Int. Med., November, 1919, xxiv, 5.



with regular daily movements of the bowels were 16 in number and averaged 183 mg. Three cases with loose, somewhat frequent movements averaged 295 mg.

In cases diagnosed as gastric neuroses of the hypersecretory variety, findings of 160, 185, 200 and 154 mg. were found. One of these cases with 440 mg. was negative in a gastro-intestinal calculus roentgen-ray examination.

A study of the gastric contents of these 60 cases showed that 28 had a high acid curve. Their average cholesterol reading was 218 mg. The normal acid cases numbered 12, with an average reading of 220 mg. Achylia gastrica cases averaged 178 mg. while those with low acid curves showed 184 mg. per 100 c.c. of blood.

In 5 chronic appendicitis cases we found 180, 190, 223, 285 and 318 mg. of cholesterol in 100 c.c. of blood. The last two were operative patients in whom the biliary apparatus was declared negative, but with the appendicular condition there existed widespread adhesions throughout the right abdomen.

The following isolated diagnoses were made in cases with their respective cholesterol readings:

Gall-bladder disease, sine calculus (operative)	{ 149
	{ 195
Rheumatoid arthritis	187
Chronic pancreatitis	248
No abdominal lesion (operative)	{ 286
	{ 147
	{ 235
Visceroptoses (2)	{ 216
	{ 210
Migraine and hypertension	100
Abdominal adhesions (operative)	

The relationship of cholesterinemia and gall-stones in our cases is shown in this table:

Gall-stones (clinical).	Gall-stones (operative).
206	250
151 } 333 }	190
250 } 280 }	200
316	
Gall-stones (roentgen ray).	Passed stones per bowel.
136	210
200 } 220 }	122
260	After passage of stones, : calculus roentgen-ray negative.
222	
284 } 160 }	
177 } 260 }	
310 } 232 }	
250 } 260 }	
270 } 182 }	

Bracketed figures represent findings in the same case.

The question of the relationship of cholesterol and gall-stone formation has been much discussed in the literature. For the most part the evidence points to an inconstant and uncertain status. Reiman and Magoun<sup>19</sup> in a study of 60 operative cases found that other upper right abdominal lesions yielded cholesterol figures almost as high as those obtained in stone cases, both averages being above normal. Gorham and Meyers<sup>20</sup> and Denis<sup>21</sup> are in accord that a cholesterol estimation has little clinical and prognostic value in calculus cases.

Obviously there is no reason to assume a hypercholesterinemia in stones of other than cholesterol composition. It must also be true that the precipitation of cholesterol cannot be a uniformly progressive procedure if it depends largely upon an exogenous origin in the blood or bile; that even though a stone were one of hypercholesterinemic origin, findings in the blood would not always show high readings for this lipid. When one subtracts the instances when stone formation has an infection or stasis origin we add still further to the instances when biliary calculi might be present without a hypercholesterinemia. If we consider the weight of gall-stones and add the amount of cholesterol in the bile, together with the length of time required for their formation, it seems only reasonable to assume abnormal conditions of crystallization and precipitation as etiologic factors. The causes of crystallization seem to be found in nuclei of bacteria or epithelial cells.

Whether a hypercholesterinemia can be caused by a lesion of the biliary system in turn due to the presence of stones is uncertain. That lesion could scarcely be anything else than an inflammatory one, and it is well known that stones may exist without inflammation, and inflammation along the biliary tree can be very extensive and severe without calculus formation. The relationship of gall-stones and cholesterol in the blood seems to be a complicated one—one which is intimately related to a complex of food, bile, blood and body tissues—their amount, chemistry, bacteriology and physical properties.

**Summary.** 1. Sixty cases presenting gastro-enterologic aspects were studied for their blood-cholesterol content.

2. Insofar as possible the clinical, roentgen ray and postoperative findings are correlated.

3. The relationship of constipation, hyperacidity and leukocytosis to cholesterol findings are considered.

4. The highest finding was 480 mg., the lowest was 100 mg.

5. Inconstant results were obtained in most of the conditions when more than one case was studied.

6. The figures for cholelithiasis averaged high (228 mg.). Other cases averaged 207 mg., both averages being above the high normal

<sup>19</sup> Surg., Gynec. and Obst., March, 1918, p. 282.

<sup>20</sup> Loc. cit.

<sup>21</sup> Loc. cit.

limit of 200 mg. The highest finding was 316 mg. and the lowest 136 mg. The highest reading in non-calculus cases was 480 mg. and the lowest 100 mg.

7. Inconstant findings were sometimes found when more than one estimation was made in the same case on different days.

**Conclusions.** From our limited studies and an estimate of the literature, blood-cholesterol seems to offer little practical diagnostic help in gastro-enterological cases.

Appreciation is expressed to Dr. Joseph Sailer for the use of clinical material and to Miss Sarah C. Hetherington for her valuable assistance.

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## A STUDY OF HYPERACIDITY.

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AND

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HYPERACIDITY is a subject which has received an endless amount of discussion. In fact the main portion of this subject has been thoroughly incorporated into the body of clinical medicine without the thorough investigation which the subject deserves. In other words the subjective symptom hyperacidity is a definite clinical entity. Less definite, but none the less fixed in the minds of the medical profession, is the belief that there exists an actual demonstrable titratable acidity. In fact the tremendous amount of clinical work which has been performed on pathologic cases has firmly fixed in the eye of the clinician the fact that high acid figures demonstrate gastric pathology. There was absolutely no evidence at hand to counteract this tendency until a more thorough research into normal gastric activity was carried out. The whole subject, therefore, reverts to the question of a comparison of normal and pathologic findings, and it requires, as a *sine qua non*, an absolute determination of gastric activity and the factors controlling it in health. We must start in with a normal conception before we attempt the interpretation of pathologic data.

We deny that most of the known information on gastric function was obtained on normal individuals, otherwise it is not possible to understand the marked discrepancies which have occurred in this line and which have occasioned so much discussion among gastro-enterologists. An individual with a gastric fistula is not a normal individual; an animal with a Pavlov pouch is not a normal animal; single studies on isolated individuals do not reveal the variations

and normal tendencies which attend gastric digestion. In fact, we know of no series of investigations previous to our own in which a large-number of normal individuals were submitted to examinations destined to reveal the whole range and variations of the gastric response to every form of foodstuff.

The results of these investigations, some of which have been published, establishes clearly the following facts, which are of extreme importance in establishing a normal conception of gastric digestion:

Every individual has a characteristic form of gastric digestion.

We would divide this statement into two parts: First, there are apparently three forms of secretory response, all of them found in normal individuals. Secondly, there are three forms of motor response also found in the same individuals. We have already described the three varieties of secretory function as hyper, iso and hyposecretory function. In other words, all individuals belong in one of these three groups, and, as a rule, an individual who shows a hyposecretory response with one type of gastric stimulus (food) will show it with another type of stimulus. About 40 per cent. of normal individuals reveal a response in the hypersecretory group and about 30 per cent. in the iso and hypersecretory groups respectively. An individual in health with conditions equal almost always runs true to type; in disease there may be marked variations, as we shall discuss in later communications. In other words a hypersecretory individual will react in hypersecretory fashion to water, bread, meats and, in fact, the whole line of foodstuffs, while the hyposecretory individual will react in hyposecretory fashion to the same stimuli.

Not only is there a definite form of reaction to a response, but there is also a more or less typical form of motor response, so that we have been able to group our cases into those who from the motor standpoint reacted: (1) rapid evacuation or rapid or quickly emptying stomachs; (2) slowly evacuating stomachs or the hypomotile types; (3) those which empty neither fast nor slow, but, are according to our conceptions, of normal function. We might divide these types into hypermotile, hypomotile and isomotile types, inasmuch as they represent ranges of normal gastric action. In other words, there is unquestionably a large secretory and a large motor range in health which must be thoroughly understood before we draw pathologic interpretations from data which may yield similar figures.

There is no question that exaggerations of almost all of these types may indicate pathology, and the line of demarcation between the end of normal findings and the beginning of pathologic manifestations is exceedingly difficult to define. Furthermore, we know that gastric pathology may exist in the presence of normal secretory and motor function or may convert one type into the other type and

still be within the range of normal function. But another interesting point is evident from these studies, namely, the fact that it is only a step from these normal findings to obviously pathologic ones. For instance the findings of the hypersecretory type may be exaggerated into pronounced hypersecretion. In discussing hypersecretion elsewhere one of us pointed out that hypersecretion, or rather a continued secretion after all digestion had ceased in the stomach, was a frequent finding in the hypersecretory normal type and that it was difficult to establish the point at which normal continued secretion ceased and pathologic hypersecretion commenced. The fasting hypersecretion, Reichmann's disease and digestive hypersecretion, are but exaggerations of the hypersecretory type, while hypersecretory findings in the other two types are at once abnormal. Likewise it is but a step from the hyposecretory normal types to the phenomena subacidity, anacidity, achylia and delayed digestion. Disease in its effects on gastric function apparently follows these steps.

The subject which we wish to discuss, however, is the question of hyperacidity, and here we are immediately met with the fact that in discussing this subject correctly we must immediately separate the symptom hyperacidity from the true hyperacidity as revealed by chemical titration. In no way does the symptom of hyperacidity as described by the patient come into this discussion. We are all of us clearly established as to the fact that the subjective symptom hyperacidity in many instances has nothing to do with titratable acidity. This symptom has repeatedly been noted in the presence of gastric achylia, and one of us has encountered many cases of demonstrable subacidity in which the patient complained of hyperacidity and was relieved by the administration of alkalies. Here we meet with a condition which is clearly a lessening of acid tolerance. One thing is clear clinically, that many subacid cases reveal this symptom, and not a few cases in which high acid figures are found are absolutely without any evidence of this finding (subjective); on the other hand a different mechanism, a marked increase in secretory velocity, with an excessive amount of unsaturated secretion (hypersecretion), may and frequently does induce this symptom. But none of these conditions are to be called true hyperacidity.

Pinning ourselves down to exact facts as revealed by the titration of the gastric contents at intervals, what then are the findings? In the first place hyperacidity clinically is taken as being present when the titratable acidity exceeds 70 to 80 (0.25 to 0.28 per cent. HCl) and yet in over 40 per cent. of our normal cases the total acidity exceeds this figure. In our series of cases the average total acidity encountered in a series of studies on foods in the normal individual was as follows:

## RESULTS OF EXAMINATION OF 924 COMPLETE CURVES OF VARIOUS FOODS IN THE NORMAL HUMAN STOMACH.

Food.	Total number of cases.	Cases with acidity of 100 or over. Number of cases.	Percentage.
Bread and cereals . . . . .	82	6	7.3
Pies, cakes and pastry . . . . .	89	35	39.3
Fish . . . . .	82	75	91.5
Meats . . . . .	203	156	76.8
Ice-cream and drink . . . . .	48	10	20.8
Eggs . . . . .	104	23	22.1
Nuts and fruits . . . . .	94	34	36.1
Tea . . . . .	139	27	19.3
Milk and cream . . . . .	47	21	44.6
Candy . . . . .	39	3	8.0

## NORMAL ACID FINDINGS (842 CURVES).

384 cases out of 842 had an acidity of 100 or over.

Acidity of 200 or over . . . . .	1 case
Acidity of 180 or over . . . . .	2 cases
Acidity of 170 or over . . . . .	4 cases
Acidity of 160 or over . . . . .	11 cases
Acidity of 150 or over . . . . .	35 cases

35 cases in 842 had an acidity of 150 or over; all of these belonged to the meat, milk and fish group.

A study of these facts enables us to make the statement that to our knowledge and in our experience there is no range of titratable acidity pathologically which cannot be found normally under certain circumstances. An acidity of 100 or over (0.36 per cent. HCl) is frequently encountered normally and is not to be construed as hyperacidity. In fact, with certain foods (notably meats and fish) the average was considerably over 100, while with other foods the secretory output was below this point. Immediately the clinical objection is interposed that inasmuch as we use one form of meal as a standard, what are the normal variations of such a meal? The normal variations with tea and toast, for example, are such as to preclude the possibility of accepting our present conception of hyperacidity as the correct one. Furthermore, while the higher acidities occur with protein foods, for example, and there is an unquestioned range of secretion and secretory output varying with different foods, the individual who may register normal acidities with carbohydrates may show hyperacid figures, with protein foods in both instances and with no evidence of gastric pathology.

These findings are so important, and have been so thoroughly impressed upon us by our work, that we do not hesitate to say that hyperacidity as expressed by an actual increase in titratable acidity over the normal range scarcely exists, inasmuch as we have obtained in our normal studies on normal men figures which overlap any obtained under pathological conditions.

This does not mean, however, the volume of the secretion, inas-

much as the total amount of acidity and not the degree of titratable acidity may vary markedly from normal findings.

Pathologically, therefore, it is evident that if the normal range of titratable acidity for a certain foodstuff is to be found within certain limits these limits may be exceeded in diseased conditions. Furthermore, it is evident that if an individual who is normally hypersecretory in type begins to show hyposecretory responses, this may be construed as evidence of the onset or presence of gastric pathology.

On the other hand very high acidities, such as 0.5 per cent. HCl, when introduced into the stomach are reduced to the gastric optimum by means of the autoregulatory mechanism, namely, the regurgitation of the alkaline intestinal secretion.

In other words, in health, while the variations in titratable acidity are very much higher than has hitherto been assumed, nevertheless, there is unquestionably this mechanism, which not only protects the organ but which ensures the presence of a gastric optimum at all times. A disturbance of this mechanism will naturally result in high acid figures, and in most cases subjective symptoms. It was the evidence which we have enumerated above which led us to publish some time ago the paper on the presence of the secretion of juice of constant acidity in man similar to that described by Pavlov in laboratory animals, and there is much to make us believe that the slow rise and fall of the curve are explained by many physical and chemical factors which alter this curve.

In the analysis of the components making up the gastric secretion we must clearly distinguish between the active digestive phase in response to food and the phase of the fasting stomach in which a very different mechanism is at work. Our work clearly establishes the fact that the digestive phase is made up of the psychic and chemical secretions. The psychic secretion begins immediately in response to the sight, taste and odor of food and continues for sixty to eighty minutes, possibly throughout the entire digestive period. In health with a mixed meal the quantity of secretion is over 200 c.c. and the average acidity in our first series of experiments with the psychic secretion was an average total acidity of 97.6 (0.35 per cent. HCl). The chemical secretion begins very early in digestion, probably in response to the absorption of secretagogues or soluble digestive products formed by the action of the existing secretion or psychic secretion on the food in the stomach; it is more persistent and continued and lasts throughout digestion, frequently persisting after food has left the stomach (postdigestive hypersecretion or continued secretion). There is clearly in response to food a marked increase in secretory velocity which only slowly reaches its height, owing to the fact that secretory velocity gradually increases and because the initial acid output is probably partially neutralized by the food. How great this is can be realized by the fact that small therapeutic doses of hydrochloric acid have no

appreciable influence on the gastric curve, and in the study of one case of anacidity more than 250 c.c. of 0.25 per cent. HCl had to be introduced into the stomach to induce a curve which at all resembled the normal one. It is therefore evident that the introduction of food is followed by the presence of marked secretory activity, a factor which is disturbed or perverted in disease. On the other hand the fasting stomach presents other phenomena. There is clearly a marked lessening in the velocity of the secretory output. Active peristole function succeeds peristalsis. The total and free acidity fall and through the patulous pylorus ready regurgitation occurs, with the increase of alkaline duodenal secretion, while in 55 per cent. of normal cases the fasting stomach shows the presence of bile. These succeeding cycles, the digestive and interdigestive cycles, follow one another in regular fashion and the factors controlling them are those enumerated above.

In conclusion we may state:

1. Hyperacidity as discussed in this article does not refer to the subjective symptoms, but the objective finding of an actual increase of titratable acidity over normal.

2. Evidence is deduced to prove that the normal individual elaborates acid figures as high as those commonly associated with pathologic syndromes, and in our experience no acid figures found in disease have exceeded the figures which we have obtained under certain circumstances in health.

3. The average acid finding during the digestion of certain foods in the normal stomach was found to be within the range which is accepted by all clinicians as abnormal.

4. There is a group of normal individuals, approximately 40 per cent., who constantly show the acid titration findings of so-called hyperacidity.

5. It is essential that our views on this subject be altered and that we accept first these normal findings as a basis for the interpretation of pathological cases.

6. The introduction of very high acidities (0.5 per cent. HCl) is followed by the activity of the autoregulatory mechanism which brings about a gastric optimum.



## REVIEWS

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A LABORATORY SYLLABUS OF CLINICAL PATHOLOGY. By CHARLES E. SIMON, M.D., Professor of Clinical Pathology in the School of Medicine and the College of Physicians and Surgeons of the University of Maryland. Pp. 86. Philadelphia and New York: Lea & Febiger.

TEACHERS of clinical pathology will find this syllabus of great value; the student will likewise appreciate the clear and explicit directions. It is not a text-book but strictly a laboratory manual, prepared by the author for the express purpose of aiding the teaching of an important practical subject and serving as a time-saver in view of an overburdened curriculum. The subject of examination of the blood, urine, sputum, stomach contents, spinal fluid, Wassermann test, blood sugar, blood urea, etc., are covered in thirty-nine lessons of about two hours each; doubtless most teachers will find it necessary to repeat portions of several lessons. The book could be improved upon by giving the subjects of the lessons in bold type in the text, in addition to the table of contents.

J. A. K.

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PATHOGENIC MICROÖRGANISMS. By WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College, and ANNA WESSELS WILLIAMS, M.D., Assistant Director of the Bureau of Laboratories of the New York Department of Health; assisted by CHARLES KRUMWIEDE, M.D., Assistant Director of the Bureau of Laboratories of New York. Seventh edition. Pp. 786; 214 engravings; 9 full-page plates. Philadelphia and New York: Lea & Febiger, 1920.

THIS book scarcely requires any further comment than the statement that it is a worthy successor of the preceding six editions; it is so well and favorably known and so widely used that nothing remains to be written about it except to commend the authors for drawing upon the valuable experience and work of Dr. Krumwiede and other laboratory associates.

Considerable new material has been added and portions entirely rewritten. The information gained during the influenza epidemic

and during the last part of the war with preventive measures against typhoid fever, paratyphoid fevers and wound infections due to anaërobies has been added. The chapters on media, immunity, streptococci, yeasts and influenza bacilli have been extensively revised, bringing the book quite well up to date and presenting the subject-matter in the clear, concise and systematized manner characteristic of all editions of this valuable book. J. A. K.

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SURGICAL CLINICS OF CHICAGO. Volume IV, No. III, June, 1920.  
Pp. 204; 79 illustrations. Philadelphia and London: W. B. Saunders Company.

THIS number is somewhat smaller than the previous ones, having fewer articles, but with the one criticism of a mistake in assembling of the book, it reaches the high standard set in the past. The error in binding spoils to a great extent two of the contributions.

The first article on empyema brings out some valuable points even on this much discussed subject. The illustrations here are also very good.

Another writer gives a very instructive contribution on the common bile duct and the means of surmounting many of its operative difficulties.

Other articles, though shorter and on less spectacular subjects, give the reader valuable points. E. L. E.

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MENDERS OF THE MAIMED. By ARTHUR KEITH, M.D., F.R.S.,  
Conservator of the Museum and Hunterian Professor, Royal  
College of Surgeons, London. Pp. 335; 23 illustrations. New  
York and London: Oxford University Press.

By weaving together accounts of the lives and of the works of eminent men of science who have advanced the knowledge of surgery during the last century and a half, Professor Keith has produced a highly interesting volume. Entertaining when viewed as a series of surgical biographies, including John Hunter, Hilton and H. O. Thomas, it is also valuable from the scientific side, for by making use of these personalities and their endeavors the author has traced the growth of our knowledge on such important subjects as degeneration and regeneration of nerves, bone-growth and bone-reproduction and tendon-transplantation. There is a freshness and vigor in the style, and the author succeeds in illumining for us many of the critical situations in surgical history from which advances

were made. To achieve this he introduces us to various workers in their hospital wards, physiological laboratories, dissecting rooms or private workrooms, and graphically delineates the environment in which they worked and the problems which confronted them. Thus we have Duchenne and his battery in the Paris hospitals, testing the action of muscles; we have Waller studying the nerve of the transparent tongue of the frog, which resulted in establishing the law of Wallerian degeneration; we have Arbuthnot Lane, at Guy's Hospital, performing his first osteosynthesis; we have Henry Head submitting to have certain nerves cut in order to follow out more closely the loss and reacquirement of sensibility. Not only, however, are we shown the bright side of the picture, for in such a retrospect it is not uncommon to find at times the ruling point of view was erroneous, and we are made to realize by what uncertain steps knowledge progresses.

There is an interesting chapter on orthopedic work in the United States. This begins with an account of John Rhea Barton, professor of surgery in the University of Pennsylvania who in 1826 introduced a new operation on a case of ankylosis of the hip-joint. This and other novel operations indicate that already in the early years of the nineteenth century there was a native school of American surgery. In passing, one notes what long periods of time some of the older men spent in the dissecting room before entering on their surgical careers, *e. g.*, John Hunter, twelve years, and Hilton, twenty years.

This, then, is a history both of men and of ideas, and this fact, coupled with the author's realistic style, will ensure a wide circle of interested readers.

W. H. F. A.

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THE MORPHOLOGY AND EVOLUTIONAL SIGNIFICANCE OF THE PINEAL BODY. By FREDERICK TILNEY, M.D., Professor of Neurology, Columbia University, and LUTHER F. WARREN, M.D., Professor of Medicine, Long Island College Hospital. Pp. 257; 97 illustrations. Philadelphia: Published by the Wistar Institute of Anatomy and Biology.

THIS memoir is the first part of a review of the recorded facts about the pineal body. Part II deals with the physiology and pathology of the organ and Part III with the clinical aspects. The chief question of interest which is discussed is whether the Mammalian pineal body is to be regarded as a vestige or whether it is an organ in some way related to metabolism. Before discussing this and other related questions the comparative morphology, embryology and histology of the epiphyseal complex are detailed. In this descriptive part, which occupies nearly 200 pages, and in which 432 titles are quoted, a very thorough abstract of the literature is

given. In the last fifty pages of the volume the significance of the various facts is closely analyzed, with the conclusion that the pineal body cannot be a vestige but is a glandular structure necessary, in some way yet unknown, to metabolism. They conclude also that there is no direct relation between the median eye of reptiles and the pineal body of mammals, and that the latter cannot be regarded as the vestigial, metamorphosed or atrophic residuum of the former.

W. H. F. A.

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PRINCIPLES AND PRACTICE OF INFANT-FEEDING. By JULIUS H. HESS, M.D., Professor and Head of the Department of Pediatrics, University of Illinois College of Medicine, etc. Second revised edition. Pp. 343; 18 illustrations. Philadelphia: F. A. Davis Company.

THERE is always need for a good book on infant-feeding. Dr. Hess's book is certainly in that class. It is not only good but it is a safe book to recommend to students and general practitioners who are not essentially pediatricists.

As usual one finds in the beginning of the volume general considerations including a discussion of the anatomy, physiology and bacteriology of the digestive tract and the metabolism of infants. In Part II the nursing and the management of the breast-fed infant are considered, and there is also a valuable chapter on premature infants. Part III deals with artificial feeding. All so-called methods of feeding are spoken of and impartially noted. Wisely, then, the author shows how they may all be used to advantage and combined in a complete study of an individual case. That is, one should know not only the calories and percentages in a mixture, but should also be aware of the number of grams of protein, fat and carbohydrate. In the last part of the book the various nutritional disturbances in artificially-fed infants are taken up in detail.

A. G. M.

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OTO-RHINO-LARYNGOLOGY FOR THE STUDENT AND PRACTITIONER. By W. GEORGES LAURENS, authorized English translation of the second revised French edition, by H. CLAYTON FOX, F.R.C.S., with a foreword contributed by J. DUNDAS GRANT, M.A., M.D., F.R.C.S. Pp. 592; 324 illustrations. New York: William Wood & Co.

It is always interesting to see the appearance of a book that endeavors to fill a new field, and the present treatise is, as far as we know, the only work devised solely for the instruction of the general practitioner who has not made oto-laryngology a special study. The

author, while instructing the general practitioner in "what not to do" and "what to do" in treatment of diseases of the ear, nose and throat, draws the line at that point where he believes a special training necessary to successfully handle this class of cases. The methods of examination are simplified and the more complicated ones only mentioned in order to show what can be done in such cases by a trained specialist. This is also true of the operative work, the minor operations being described in sufficient detail to enable their successful carrying out by the general practitioner, and the more complicated procedures simply mentioned. Yet we must admit that in trying to simplify the technic and methods used in the examination and treatment of diseases of the nose, throat and ear the author has perhaps in some instances overstepped the boundary and in others given what seems to us unwise advice. For instance the suggestion that deafness may be properly treated by the general practitioner, when it is admitted that a proper diagnosis of the condition requires special training, would seem to us pregnant of distinct harm. Also some of the operations which he describes such as the blocking of the superior laryngeal nerve for the pain of laryngeal tuberculosis, had much better be left to the specialist. Again, the advice that the removal of tonsils with punch forceps "is a method so simple as to be within the power of every doctor to practice" is very bad advice.

The ground covered is very extensive, and there is little doubt but that the usefulness of the average practitioner will be greatly enhanced by the reading of this work, and we believe that H. Clayton Fox, in translating it into English, has brought an important contribution to the medical literature of this country. The illustrations are largely diagrammatic, but numerous and exceptionally illustrative.

G. B. W.

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DISEASES OF THE THROAT, NOSE AND EAR. FOR PRACTITIONERS AND STUDENTS. By W. G. PORTER, M.B., B.Sc., F.R.C.S. (Edin.). Third edition, fully revised under the Editorship of A. LOGAN TURNER, M.D. (Edin.), F.R.C.S. (Edin.); Consulting Surgeon, Edinburgh Eye, Ear and Throat Infirmary, etc. Pp. 300; 79 illustrations, 44 of which are in colors. New York: William Wood & Co.

THE second edition of this little manual was published while the author was in active service with the British Army in 1916, the revision being undertaken by Dr. P. McBride. Major Porter, D.S.O., was killed in action in 1917 and the present edition has been carefully rewritten by Drs. J. Milne Dickie, J. S. Fraser, Douglas Guthrie, W. T. Gardiner and A. Logan Turner, which fact should speak for itself as to the value of the work.

It is essentially a book for the general practitioner, the senior student and the non-specialist, the major operations not being described in detail, the indications for their performance and their general features alone being given. Anatomical descriptions and illustrations of instruments have been omitted, which is a commendable feature in a work of this kind. It is a good type of working manual, of the old-fashioned kind, brought up to date, and should retain the popularity of the two former editions. G. M. C.

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SURGICAL CLINICS OF CHICAGO. Vol. IV, No. 2, April, 1920. Pp. 222; 79 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

AGAIN it is the pleasure of the reviewer to say a good word for the *Clinics*. This number, though smaller than the average, is equally as good if not better than some of the preceding volume numbers. The same high standard is maintained in both the contributors and the subject-matter.

The *Clinics* is famous for the variety and interest of the subjects. In fact very often one gets a much more interesting and instructive grasp of a subject read here than he could obtain from a text-book.

The number is full of excellent ideas.

E. L. E.

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PASTEUR. THE HISTORY OF A MIND. By EMILE DUCLAUX, late member of the Institute of France, Professor at the Sorbonne and Director of the Pasteur Institute. Translated by ERWIN F. SMITH and FLORENCE HEDGES, Pathologists of the U. S. Department of Agriculture. Pp. 363; 35 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

NOT the least interesting part of this delightful volume is the introduction. Here the translators give the life history of the author, Duclaux-Ducleaux, the pupil and friend of Pasteur, in himself a genius. The first part of the book proper deals with the predecessors and teachers of Pasteur, Haüy, Weiss, Delafosse, Biot and Herschel, and shows how Pasteur acquired the taste for researches of a certain type. Altogether there are eight parts to the book, each divided into its component chapters, and comprising in the main the following subjects: Works on crystallography; lactic and alcoholic fermentations; spontaneous generations; wines and vinegars; studies on the diseases of silkworms; studies on beer; studies on the etiology of microbial diseases and the study of viruses and vaccines. Most interesting are the studies on silkworms.

In these pages, as elsewhere in the book, one may follow the workings of Pasteur's mind, or at least the analysis of thought and motives as elaborated by Duclaux. The study of viruses and vaccines, including the chapters on rabies is absorbing. Throughout one is held by the fact that one receives not only the results of successful research, but the pathways leading to success are mapped out and detailed, and the failures and mistakes of a great intellect are impartially laid bare.

A. G. M.

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PERSONAL BEAUTY AND RACIAL BETTERMENT. By KNIGHT DUNLAP, professor of Experimental Psychology in the Johns Hopkins University. Pp. 95. St. Louis: C. V. Mosby Company, 1920.

THE author presents for consideration a conception of beauty which differs from that found in poetry, song and romance. Beauty is of importance from the point of view of the race and of civilization. In the detailed character of beauty, stature, bodily proportions, features, hair, fat, muscular tonicity and poise are considered. (Incidentally it may be saddening to the reader to see that lack of the pate-hair is a fatal bar to beauty.) The combination of these characteristics is the expression of the potentiality of the individual and shows what he is capable of doing for the species. The most beautiful woman and the handsomest man are the persons we would choose to be coparents of our children. The procreation of children is considered the predominant ideal in marriage. Human beauty is a sign of fitness for parenthood. The conservation of beauty is the problem of the present day and of all time.

These, in brief, are some of the main points brought out by the author. Prostitution, the effect of war, the stage and other factors are discussed in their relationship to beauty and sex-selection and breeding.

A. G. M.

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THE OPIUM MONOPOLY. By ELLEN N. LA MOTTE. Pp. 84. New York: The Macmillan Company, 1920.

MISS LA MOTTE's small book is an interesting statistical study of the opium production and sale in various English colonies. She makes out a rather strong case against the British Government's monopoly and open sale of this insidious drug. A large number of Englishmen recognize the immorality of the opium trade which flourishes under the British flag. The evil is well recognized in England. As such is the case it does not seem to be appropriate for an American to write a diatribe against a trade which is totally English and of which enlightened Englishmen are well aware and against which they have frequently protested. It does not seem

incumbent upon us Americans at any time, and particularly at the present time, to call attention to any moral obliquity which exists in England and her colonies. Nor does it seem that Miss La Motte has presented sufficiently strong evidence against the opium trade to warrant the publication of a book such as this, written by an alien. Furthermore, there are enough evils existing in this country, and no one who has read *The Backwash of War* can fail to appreciate that the author is well able to ferret out and to discover all that is disagreeable, for the correction of which Miss La Motte could apply herself with greater advantage than attempting to judge the turpitude of other nations.

J. H. M., Jr.

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PRINCIPLES OF HUMAN PHYSIOLOGY. By ERNEST H. STARLING, M.D., Jodrell Professor of Physiology, University College, London. Third edition. Pp. 1315; 579 illustrations. Philadelphia: Lea & Febiger, 1920.

THIS third edition of Starling's *Physiology* is generally well balanced in presenting the various phases of the subject from the underlying physical and chemical basis to the outlying topics, which are far-reaching in clinical application. The introduction epitomizes the text in considering the phenomena of living matter as based on adaptations which are reactive "adjustments of internal to external relations." Topical arrangement of the text gives general physiology 164 pages, mechanisms of movement and sensation 462 pages, mechanisms of nutrition 608 pages and reproduction 48.

Characteristic features of marked value are frequent paragraphs on comparative anatomy and physiology, full illustrations by excellent diagrams, notably of nerve pathways and consideration of general physiology. Discussion of practical topics gives evidence of scope and up-to-date character, *e. g.*, defence of the organism against infection, nourishment and protection of the eye, referred pain, spinal shock, speech, voice-production, vitamins, etc. In a masterly manner, both as regards text and illustration, Dr. H. Hartridge revises the section on sense organs, and is entirely responsible for the chapters on vision. But fifty additional pages allotted to vision tend to overbalance other equally important topics. One wonders when it appears first among the senses whether the innovation is to honor the writer or the function. Starling's distinguished investigations in the field of nutritional mechanisms account for the especially scientific presentation of these subjects. He includes latest developments in regard to functions of each system often adding interest with descriptions of methods and apparatus by which experiments are made.



In the preface the author generously asks for suggestions that will make the book more useful. The present reviewer emphatically suggests enlargement of the index by more complete crossing to save time; addition of references to stimulate reading and frequent insertion of dates to vivify the text and add perspective.

Those who already know Starling's *Physiology* are grateful for this splendid revision. New readers, whether students or physicians, will have a treat, for this book is a storehouse of information in regard to fundamental facts and theories with their practical applications presented in most acceptable form. R. W. L.

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HANDBOOK OF DISEASES OF THE RECTUM. By LOUIS J. HIRSCHMAN, M.D., F.A.C.S., Detroit College of Medicine. Third edition. Pp. 378; 227 illustrations, 4 in color. St. Louis: C. V. Mosby Company, 1920.

A BOOK written essentially for the general practitioner, yet from the authority of a specialist; a book covering a field of work that every physician meets daily, yet in which he is so often completely at sea; a book detailing the office technic in its simplest, safest and surest form, yet from the knowledge of one with vast experience; outlining the surgical procedure in harassing conditions that are too often treated in a palliative way, yet are in truth easily amenable to cure under a local anesthetic; a book illustrated so copiously that the pictures alone tell all the essential steps, yet with a text that is delightful reading. Such is Hirschman's *Handbook*, and its appearance in its third edition is welcomed. Hirschman states that 75 per cent. of the surgical operations about the anus and lower rectum can be made easy office procedures if one but follows the technic of local anesthesia he gives. The chapter on constipation is excellent. Pruritus, ulcer, fissure, fistula, abscess, hemorrhoids, inflammations and polypi are all splendidly presented. It is a pity that the chapter on dysentery has been entrusted to other hands, for though the subject is covered by an authority its diction is very poor and in places ambiguous. We would suggest, as a minor criticism, that in subsequent editions the chapter on anesthesia be placed nearer the front of the book and so eliminate reiterative reference, and that the various operative methods advised for hemorrhoids be more clearly differentiated in the text. The author need not apologize for his specialty. His book should command the greatest respect and be to anyone a valuable reference volume. A. R.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
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**Habitual Dislocation of the Shoulder.**—OLLERENSHAW (*Jour. Orthop. Surg.*, 1920, ii, 255) reports very briefly 4 cases, one of which was operated on before he saw it but nothing is said of the particular operation performed or its results. He did the Clairmont operation on 3 of the cases. This operation provides a muscle flap fashioned from the deltoid which is passed around the head and neck of the humerus and acts as a sling to brace the head and keep it in the socket. All 3 cases were operated on in the past year which does not entitle him to refer to them as permanent successes. He intends to deal with any future cases by this muscle flap operation and at some future date to report on all such cases including those referred to in this paper. He tells of a paper by Armour read before the Liverpool Medical Society in 1914 in which 2 cases operated on by this method were reported. In the first the dislocation recurred a few months later. The second had had no dislocations since the operation. In the discussion which followed Ollerenshaw's paper, Dunn said he had seen a good many operations done for this condition and that in his experience excision of a portion of the capsule or plication of it has not infrequently been followed by recurrence. In one such case Clairmont's muscle flap operation gave a good result. One case upon which he did a Clairmont operation, fifteen months before, recovered completely free motion of the joint and was discharged three months after operation. He has not heard from this patient since. Bristow said that he had done this operation on the right shoulder of an epileptic which had been dislocated eighteen times, the left shoulder having been dislocated sixteen times. The operation had been done six months before and since then he had several fits and dislocated his left shoulder four times but the right had not since come out. Since then he has operated on the left shoulder as well. He attributes the good results of the operation to the big lump of ragged muscle placed under the capsule strengthening the part and to the effect of the hemor-

rhage which leads to the formation of fibrous tissue. He is not inclined to give much credit to the special action of the transplanted slip of muscle. Platt did this operation five years before on a professional acrobat and no dislocations followed the operation, but he had lost so much deltoid that his shoulder-joint musculature was incapable of bearing the full brunt of his gymnastic maneuvers. He entered the army, but Platt believed in a comparatively low category. Threthrowan plicated the capsule in 2 cases, in 1 twelve months and in the other fifteen months before, and he had not heard that they had relapsed since.

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**Pseudomyxoma Peritonei.**—BIGGS (*Ann. Surg.*, 1920, lxxi, 619) says that this condition may be described as an inflammation or irritation of the peritoneum, caused by the discharge of the epithelial lining and the contents of a pseudomyxomatous cyst of the ovary or appendix, and resulting in the production of pseudomucin and secondary tumor formation. He thinks that the most tenable theory as to etiology is that of cellular implantation: the epithelial cells lining the cyst, together with the pseudomucinous content of the cyst, being discharged through a rupture of the cyst wall into the peritoneal cavity, the cells there functioning as they did in their original situation. Five cases are reported with the operative and pathological reports in each. He concludes that the condition is much more common than is generally recognized. Caused by cellular implantation it is histologically benign, but may be clinically malignant. If it is considered to be a form of cancer, it must be assumed that pseudomucin inhibits its destructive power. It may originate in the ovary or the intestinal tract; ovarian origin being by far the most frequent. If it is appendiceal in origin, the appendix has been the seat of chronic inflammation. Early invasion of the peritoneum is characterized by a pebbly appearance. In early cases the condition will sometimes be cured, and at any stage it may be inhibited, by operation.

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**Birth Paralysis.**—PLATT (*Jour. Orthop. Surg.*, 1920, ii, 273) reviewed the literature in an effort to arrive at a working hypothesis in dealing with these cases and particularly in our teaching. He has had 23 cases of birth paralysis and in analyzing them he makes four groups. In group 1, in which there were 12 cases, the actual paralysis had recovered and the patients presented the typical subluxation of the shoulder-joint with a fixed internal rotation curvature of the arm. The mechanical disablement was due simply to the torsion and the general underdevelopment of the limb in length and caliber according to the length of time the disability had existed. Group 2, in which there were 6 cases, showed a typical subluxation of the shoulder-joint combined with a residual paralysis affecting the extensors of the wrist, fingers and thumb. The paralysis in the extensor group of muscles recovered under postural treatment in 4 out of 6 cases. In group 3 there were 3 cases which showed varying grades of paralysis. In two the paralysis was observed later to have disappeared completely. In group 4 there were

2 cases which showed exceedingly flail limbs. In one the right arm was profoundly wasted as seen in anterior poliomyelitis and there was the usual downward subluxation of the head of the humerus. Platt performed an arthrodesis in this case. In the second patient, a girl of eighteen, the left arm showed profound atrophy and lack of development in the left upper limb with a flail shoulder and wrist-joint. Platt explored the plexus above the clavicle in this case but found no trace of any lesion in the supraclavicular triangle, the nerve cords being intact but small and on stimulation giving results identical with the clinical findings. He experimented on stillborn full-time fetuses, employed all varieties of violence embodying the maneuver of separation of the shoulder from the head both before exposing the plexus and after. He failed to rupture any cord in any experiment, and on the closest inspection was unable to see any evidence of rupture of the nerve sheath. With excessive force he was unable to produce any dislocation of the shoulder-joint, separation of the epiphysis or in fact any demonstrable lesion of the shoulder-joint capsule. After weighing the clinical evidence he concludes that there is a certain amount of evidence in favor of including under the head of birth palsy two distinct groups of lesions. Under treatment he suggests that before the supraclavicular plexus is exposed in a case of birth palsy there should be in addition to complete paralysis of a muscle group which has persisted for more than twelve months, definite wasting such as is seen in true complete nerve injuries.

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**Compression Fractures of the Lower End of the Radius.**—STEVENS (*Ann. Surg.*, 1920, lxxi, 594) says that fractures of the lower end of the radius (so-called Colles) are always compression fractures, the compressive side breaking first, literally collapsing. The first point of fracture is the point of greatest compression upon the cortical surface of bone because the stress increases both in compression and tension the further away from the neutral axis. It breaks in compression because the compression is much greater than the tension. Green bone reacts to strain like wet timber. It breaks at the lower end of the radius because there are several forces, and the resultant is on the lower end of the radius posteriorly. This is due to direct compression from above, the hammer blow from below, the resistance both to compression and to blow being not in the center of gravity, but excentric to it and, therefore, increasing the strain. It is also due in part to the velocity of stress and the molecular inertia of material. The compression fractures of the lower end of the radius show the evidence of compression. There is actual loss of substance but no impaction. Breaking up of the impaction (so-called) cannot restore the planes of the articulation, nor does it do so. It might be possible by traction over a long period of time to separate this crushed surface and permit its being filled in by new bone, thus replacing the planes of the articulation, but to do this would be to sacrifice some of our chances of securing a freely movable joint. Early reduction followed by early passive and active motion will return all or nearly all compressive fractures of the radius to useful light occupation within twenty-days. Any retentive apparatus other than a leather wrist strap after ten to twelve days is contra-indicated except in a very rare instance.

**Finger Exploration of Gunshot Wounds of the Brain.**—TOWNE and GOETHALS (*Ann. Surg.*, 1920, lxxi, 531), from a careful study of 28 cases and of the literature, concluded that the entry of a foreign body into brain tissue causes irreparable damage to a more extensive area than that involved in the actual tract of the foreign body, and this cavity is further broadened by hemorrhage; hence the size of the metallic fragment or of the dural aperture is not a true index to the wider area of damage represented by the brain cavity. When such a cavity is not over 7 cm. deep and large enough to admit a finger, cleaning with forceps under careful finger control gives absolute insurances against sepsis, and only very rarely causes increased cerebral trauma which is slight and recoverable. Cleansing of such a cavity by Cushing's method of catheter palpation is sometimes not complete and therefore does not always prevent sepsis; it necessitates a prolonged operation; and it is successful only in the hands of those who have had a large experience in its technic. Brain wounds not suitable for finger palpation must be cleaned as well as possible by the catheter method, curettage, or magnet extraction, or a combination of these methods. The tendency of the difficult catheter technic to make this a special field, which requires that the wounded undergo delay if a trained neurological surgeon is not at hand, is not for the best interests of the patient, who is put under increasing risk of encephalitis with every preoperative hour. Brain wounds, and especially those suitable for finger palpation, are easy to clean rapidly and successfully if a few proper instruments are available. Any surgeon fitted to do front line work can quickly acquire the technic and do these cases in well under an hour; and, with experience in judging which casualties are inoperable may well succeed in evacuating 75 per cent. or more of his operated cases.

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## THERAPEUTICS

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UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

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AND

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**The Effect of the Subcutaneous Injection of Adrenalin Chloride on the Heat Production, Blood-pressure and Pulse-rate in Man.**—In a series of 73 experiments on patients suffering from various disorders of the ductless glands, SANDIFORD (*Am. Jour. Physiol.*, 1920, li, 407) found that adrenalin chloride (0.5 c.c. of 1 to 1000) injected subcutaneously invariably caused an increase in the metabolic rate, usually accompanied by an increase in ventilation and respiration rates, number of heart-beats per minute, volume of each beat and a greater utilization

of the blood-carrying power and peripheral dilatation, with an increased systolic and decreased diastolic blood-pressure. No relationship was found between the intensity of the adrenalin reaction and the degree of hyper- or hypothyroidism. The author found a metabolic rate curve following the injection of adrenalin similar to that found by Lusk from a carbohydrate plethora, and suggests the possibility that the increased heat production is due to an excess of carbohydrate metabolites. In addition there may be a direct stimulation of cellular combustion.

**The Results of Protective Inoculation Against Influenza in the Army at Home, 1918-1919.**—LEISHMAN (*British Med. Jour.*, February 14, 1920, p. 214). The vaccine formula recommended by a conference of bacteriologists, of which Leishman was chairman, was as follows: *B. influenzae*, 60 millions; streptococci, 80 millions; pneumococci, 200 millions per c.c. Several strains of each organism were used. Two doses were given, the first 0.5 c.c., and the second, after ten days' interval 1 c.c. The following table is a summary of the results obtained:

	Inoculated.	Non-inoculated.
Number . . . . .	15,624	43,520
Incidence of attack per 1000 . . . . .	14.1	47.3
Incidence of pulmonary complications per 1000 . . . . .	1.6	13.3
Deaths per 1000 . . . . .	0.12	2.25

Later, as the etiological role of Pfeiffer's bacillus came more and more into prominence, the vaccine formula was revised so that each cubic centimeter of the vaccine now in use contains 400 millions of *B. influenzae*.

**Intravenous Protein Therapy.**—The principal "foreign proteins" employed intravenously by Gow (*British Med. Jour.*, February 28, 1920, p. 284) are peptone and emulsions of the coli-typhoid group of organisms, the protein-complex of this group being the most efficacious in inducing the "protein shock." He has also used autogenous vaccines in pyelonephritis with good results. Within fairly wide limits the size of the dose of killed *B. coli* vaccine has little effect on the severity of the reaction. The initial dose may be between 50 and 100 millions. The reaction induced by peptone is proportional to the dose; he gives from 5 to 10 c.c. of a 10 per cent. solution. He describes in detail the technic of administration and the reaction of the patient: rigor, abdominal distress, fever, drop in blood-pressure, decrease in the number of the white blood cells followed by a rapid increase to a maximum of 20,000 to 30,000 per c.c. There may be dyspnea and cyanosis, which are speedily relieved by the hypodermic injection of adrenalin or atropine sulphate. Usually most of the symptoms have subsided by the seventh hour, the temperature returns to normal within twenty-four hours; occasionally facial herpes develops two or three days later. The principal types of cases benefited are: Infective diseases in which the infective organism is known and in which the vaccine is given for specific and "shock" effect. Those in which the causal organism is unknown

(rheumatic fever, etc.). Here the protein treatment is given solely for its non-specific effect. Those in which the causal organism is known (pneumonia, gonorrheal arthritis, etc.), but in which specific vaccine therapy is of little value. Here, too, the vaccine is given entirely for the shock effect. Chronic disorders of doubtful or unknown etiology (psoriasis, bronchial asthma, etc.). In pyogenic affections, both local and general, intravenous vaccine therapy is of value. In septicemia it is difficult to produce a rigor with a plain or sensitized vaccine alone. As the ultimate results are better when such a reaction occurs, Gow recommends the simultaneous subcutaneous administration of anti-streptococcus pyogenes serum. This renders the reaction more likely to ensue, possibly owing to the more rapid liberation of endotoxin. He has given peptone intravenously in conjunction with sensitized vaccine subcutaneously in streptococcal septicemia, and is convinced of its beneficial effects. In conclusion, Gow states emphatically that even in those diseases in which it is of value, intravenous protein therapy is to be regarded solely as an accessory to other remedies.

**Anemias of the Hemolytic Group.**—WARD (*Proc. Roy. Soc. Med.*, 1919, xiii, Sec. Med., p. 1) believes that there is a group of anemia, or of morbid states without anemia characterized by (1) familial, hereditary or any congenital tendency; (2) paroxysmal course; (3) changes in erythrocytes; (4) due to changes in plasma; (5) tending to make red blood cells more easily destroyed. The diseases, with the exception of hemolytic jaundice, are rare. They are (1) congenital hemolytic jaundice; (2) Dresbach's syndrome; (3) Herrick's anemia; (4) Malin's syndrome; (5) Clough and Richter's syndrome. (I) Hemolytic jaundice, as is well known, is either familial, hereditary or congenital. The acquired type differs somewhat but is more like the familial type than any other disease. Paroxysms of hemolysis are usually observed. The erythrocytes are more fragile than normal and there is an abnormal number of reticulated cells. No absolute proof of plasma changes has been demonstrated. (II) Dresbach's syndrome consists of the presence of elliptical erythrocytes in a healthy man. Three such instances are known. There is no anemia. Bishop's two cases were children of the same family. (III) Herrick's anemia, the so-called "sickle-cell" anemia, has occasionally been familial in occurrence. The course is paroxysmal with acholuric jaundice. The plasma of some of these cases produced similar changes in the red blood cells of the father's blood. All the patients were negroes or mulattoes. (IV) Malin's Syndrome: The characteristic feature is anemia with splenomegaly and the presence in the blood of active phagocytes. Only three cases are on record. The white blood cells increase in number and the red blood cells decrease in number, with progressive splenic enlargement. The relation to leukemia is not known. Both red blood cells and white blood cells are devoured by the phagocytes. (V) Familial auto-agglutination was described by Clough and Richter occurring in a mother and daughter. No other evidence of hemopoietic disease was present. Group Pathology: There is a primary disturbance of the plasma, which may alter the reaction of the red blood cells to hemolysis or change their shape or alter their humoral reactions in some unexplained way, thus allowing auto-agglutination or phagocytosis.

**Tuberculous Empyema.**—DUHOFF (*Am. Rev. Tuberculosis*, 1919, iii, 590) reports on 20 cases of tuberculous empyema observed among 902 patients (2.2 per cent.). Among these patients 48 were treated by artificial pneumothorax and 10 of these developed a tuberculous empyema. The onset is usually sudden, due to rupture of the lung. The temperature rises and there is pain and dyspnea which lessen as the effusion appears. Symptoms of toxemia and fever may be strikingly absent for many months. There is usually a well-marked pulmonary lesion. Dyspnea is usually absent after the initial reaction. The condition may be latent for years. In this series four ruptured into a bronchus and six burst through the chest wall. Diagnosis depends on study of the pleural fluid in which *B. tuberculosis* is usually easily demonstrable. At times acid-fast bacilli are found although guinea-pigs are not infected. Prognosis is bad but duration of life depends on the amount of pulmonary involvement and on the presence of complications as well as on the patient's resistance. Treatment: The author has tried many kinds but thinks the patients do better when let alone, unless there are reasons for relieving pressure symptoms. Thoracentesis may often be followed by a persistent sinus. When symptoms are marked and there are rapid cachexia, high fever, etc., rib resection and drainage offer the only chance of prolonging the patient's life. The author states that the fluid is pus or seropus, due to infection of the pleural cavity by *B. tuberculosis*, caused usually by lung rupture often following artificial pneumothorax.

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**A Preliminary Study of Clinical Activity.**—BROWN, HEISE, PETROFF and SAMPSON (*Am. Rev. Tuberculosis*, 1919, iii, 612) attempt to define clinical activity as that state in pulmonary tuberculosis in which pathological activity is not latent but is producing through the actual and immediate absorption of poisons certain clinical or laboratory manifestations of disease, which disease may in turn be progressing, stationary or even for the time-being retrogressing. If tubercle bacilli are present in the sputum, clinical activity is three times as likely to occur if rales are present, but even then only one-half of these are clinically active. If tubercle bacilli are not present, then clinical activity occurs in only one-fifth of the cases irrespective of whether rales are present or not. In cases without rales as many patients are clinically active when tubercle bacilli are absent as when present. In eleven (44 per cent.) of the 25 cases without tubercle bacilli only a peribronchial or questionable parenchymatous lesion was found. Of these 11 cases, 6 had hemoptysis, 1 had tuberculosis of the eye and 4 had pleurisy. As far as could be ascertained clinical activity does not vary whether sputum is present or absent. Whether rales are present or absent in patients with or without sputum is also of no importance.

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**Concerning Sensory Localization in the Cortex.**—La question des localisations sensibles de l'écorce et le syndrome sensitif cortical. PIERON (*Rev. de méd.*, 1919, xxxvi, 129) has very thoroughly reviewed the literature concerning sensory disturbances following cortical lesions and has abstracted 21 cases and presented 3 new cases. The case records and



discussion of earlier views may be read by those interested in the subject. The author concludes: "The war wounds have shown that the sensory areas of the body are in the post-central gyrus and that all types of sensation are thus represented in a very small area. Distinct topography of the post- and preaxial halves of the extremities is present. The perceptive functions, dependent on associative phenomena in the sensory cortex, are very easily disturbed by diffuse lesions. Various modalities of sensation are more easily disturbed than others, dependent somewhat on the nature of the lesion. In grave lesions the anesthesia may be complete. In less extensive lesions the sense of position and movement is usually more disturbed than the other modalities of sensation, although these too are often altered in varying degree. There is thus no pathognomonic dissociation of sensation due to cortical lesions, although the syndrome of Verger-Déjerine is the most constant. The syndrome thalamique differs from the cortical syndrome, if viewed only from the sensory standpoint, by the different behavior of the sense of pain and by the affective reaction of the patient, produced by the sensory changes."

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**Meningococcemia Without Early Meningeal Involvement.**—RIBIERRE HÉBERT ET BLOCH (*Ann. de méd.*, 1919, vi, 341). The authors report 5 instances of prolonged intermittent fever in which the meningococcus was grown from the blood and 2 other cases not proved bacteriologically but probably belonging to this group. The symptomatology varied markedly. The fever, as a rule, is intermittent, with frequent chills, at times resembling charts of malaria patients. Eruptions, usually of papulo-erythematous type, are common. Usually a few new spots occur after a high rise in temperature. They may appear on any part of the body but are most frequent on extensor surfaces of knee and elbow and on forehead. Arthralgias and myalgias are as frequent as fever and efflorescence. The commoner joints affected are knee, elbow and ankle. The joints often become red, swollen and tender. Persistent myalgia is not infrequent. Most observed cases of meningococcus septicemia have terminated by meningeal involvement. Three of these cases presented meningeal involvement after the first, second and third months respectively. In some of the cases the cerebrospinal fluid showed increased cells and globulin, which, however, disappeared quickly when small doses of serum were injected. In 1 case an endocarditis of the aortic valves developed which was due to the meningococcus and quickly terminated fatally. The duration of the disease varied from fifty to one hundred and thirty days. The general condition of the patient remained good, as a rule, in spite of the high fever. Cultures of blood should be made in ascetic bouillon or egg bouillon. In 2 instances the organism was agglutinated by antimeningococcus serum and in 3 instances by antiparameningococcus serum. The cases were treated, as a rule, by specific antisera in large doses, both subcutaneously and intramuscularly. Two of the cases died. One of endocarditis and one during a chill.

## PEDIATRICS

UNDER THE CHARGE OF

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**Gonorrheal Infection in Childhood.**—BLAND (*New York Med. Jour.*, March 20, 1920) points out that gonorrheal infection in little girls is extremely common, but it is obviously impossible even to guess how frequently this disease really occurs. Guiteras considers that 75 per cent. of the cases of vulvovaginitis is due to gonorrheal infection. Saprophytic organisms cause the remaining 25 per cent. of cases. In the great majority of the cases of vulvovaginitis the infection is indirect and is often conveyed through ignorance or carelessness. The forms and methods of conveyance are innumerable. The clinical thermometer is said to form a common medium of transfer. Underclothing, bed linen, napkins, towels, sponges, wash cloths, syringes, bath tubs, and even bath water may be the medium of contamination. The majority of cases occur in early life usually between the second and tenth years. In most cases the systemic and local symptoms of vulvovaginitis are moderate and the course of the disease is also relatively mild. The constitutional reaction to the disease is not commonly observed by the physician as they have usually disappeared by the time that the patient appears for treatment. The child usually complains of itching. There is also burning and stinging which is usually aggravated by urination. This may cause a voluntary retention of urine. Shortly after the onset of the disease the discharge appears. At first it is thin and ichorous; later it becomes thick, yellow or yellowish green, and profuse. In the still later stages it becomes mucoid, creamy or watery. The diagnosis should be made first by a careful analysis of the clinical history, second by painstaking physical examination, third by a microscopic examination of the discharge, and fourth by a serological or complement-fixation test. In the treatment prevention should be emphasized. This is especially imperative in institutions. In the prophylaxis the most important point is the examination of the vulvovaginal secretions of all female children. When the disease appears isolation is most important. This should include instruments, linens and utensils as well as a physical isolation of the individual or individuals. The author begins active treatment gently so as not to upset the small patients. His first step is irrigation with a non-irritating solution such as boric solution or preferably sterile water. After the confidence of the child is gained he employs Lugol's iodine solution in warm water. The solutions are applied through a number four soft rubber catheter. He begins with a weak solution, usually a quarter of a teaspoonful to 2 quarts of water or about a quarter of 1 per cent. solution. This is gradually increased until the strength reaches 1 per cent. Not less than one gallon of solution is used at a sitting. This is done morning and evening for three or four weeks. Once a day about 15 minims of a 25 per cent. solution of argyrol is instilled into the vagina with a medicine dropper.

At the same time the vulva is painted with the same solution and a pad of cotton saturated with the same is applied to the labia and vestibule. After four to six weeks the irrigation is used only once a day. Treatment is continued until four successive negative smears are obtained and until the complement-fixation test is negative.

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**Prognosis in Operated Cases of Hypertrophic Stenosis of the Pylorus.**—GOLDBLOOM and SPENCE (*Am. Jour. Dis. Children*, April, 1920) base their report on a study of 163 cases operated by the Rammstedt method during a four-year period. They found that the duration of symptoms prior to operation was probably the most important single factor affecting the prognosis. When symptoms had lasted less than four weeks the mortality was one-third as great as when they had lasted four weeks or longer. The mortality-rate in artificially-fed babies was more than three times that for breast-fed babies. In infants weighing seven pounds or less the mortality was three and a half times greater than in those whose weight exceeded seven pounds. The mortality increased in direct proportion to the amount of weight lost previous to operation. The mortality for breast-fed infants who had vomited for less than four weeks, and who had lost less than 20 per cent. of their best weight, was almost nil. The fatalities which occur are due to accidents which are avoidable when the operation is done by a skilful surgeon.

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**The Clinical Role of the Fat-soluble Vitamin: Its Relation to Rickets.**—HESS AND UNGER (*Jour. Am. Med. Assn.*, January 24, 1920) say that it would lead too far away from the subject to discuss the various theories that have been advanced to account for the occurrence of rickets, and as the data are not adequate no definite conclusion can be made. There seem to be several causes at work, rendering the unravelling of the problem so difficult that there is a difference of opinion not only as to the particular dietary factor that is at fault, but even as to whether rickets is to be considered a disorder of dietetic origin. It should not be lost sight of that there is a prenatal factor involved. The fact that the negro infant, living side by side with the white in the larger cities and obtaining milk from the same source, develops rickets so frequently and so markedly, indicates that there are important influences to be reckoned with in addition to the food. In considering the diet a most important question is whether the recent theory as to the vitamin origin of this disorder can be maintained, and, more particularly, whether rickets should be attributed to a lack of the fat-soluble vitamin. The clearest understanding of this aspect can be obtained by comparing this disease to the well recognized and established deficiency diseases, scurvy and beriberi. By comparison it is shown that these two disorders are commonly manifested by weakness and inanition, and there are not the fat apparently healthy babies seen in rickets. The most important thing is the fact that neither can be brought about by overfeeding. Rickets frequently develops in infants, receiving too much milk rich in fat, proteins and salts. It is impossible to make this fact go with the thought of a deficiency disease. The studies of the authors show that the fat-soluble vitamin is not the controlling influence. They also show that infants develop rickets while receiving a full amount of this principle, and that they do mani-

fest signs, although deprived of this vitamin for many months, and at the most vulnerable period of their life. They do not find it possible to accept the term "fat-soluble vitamin" as synonymous with "anti-rachitic factor." They say that the danger to infants of a diet deficient in fat-soluble vitamin is slight, provided it contains a sufficient amount of calories and is complete in other ways. The infants can maintain their health and vigor in spite of taking in amounts of fat-soluble vitamins so small that they are rarely encountered in ordinary times. In spite of the fact that this vitamin is not widely distributed in nature, a disorder that may be termed "fat-soluble deficiency"—marasmus or xerophthalmia—is hardly to be appreciated from a clinical standpoint. The study of rickets was undertaken on 100 children in a modern child-caring institution. These infants lived under excellent hygienic conditions, their nursing and care was the same, their food was prepared in a central diet kitchen, and they remained in the institution for the entire period of observation. Once a month they were examined for rickets. This included a notation as to the size of the fontanelle, the beading of the ribs, the enlargement of the epiphyses, the condition of the musculature, the eruption of the teeth, the static development and the like. They were placed on various diets; an abundance of fat and fat-soluble vitamin in the form of milk and cream, a deficiency of these substances as in skimmed milk, and abundance of water-soluble vitamin as in autolyzed yeast, and diets such as Mellin's food or condensed milk. In all cases there was but one deficiency in the diet, which was adequate in quantity and therefore in its caloric value, and contained in every case sufficient antiscorbutic foodstuff. They realize that a test of this kind should be carried out for years and consequently it is impossible to lay down absolute conclusions. They were able to draw some conclusions. They call attention to the fact that the laboratory results are absolutely at variance with the opinions of most clinical observers, who believe that rickets follow overfeeding. There is no delicate indication of what may be termed latent rickets or subacute rickets. This can only be recognized by metabolism tests. After a preliminary study they found that beading of the ribs, especially in conjunction with the enlargement of the epiphyses, furnished the most reliable criterion of the course of the disease. It was found that six grades of beading could be distinguished. Physicians in general and pediatricians in particular, regard beading of the ribs as a pathognomonic sign of rickets. The writers noted that there was also a marked beading in infantile scurvy, but that the beading became rapidly less or disappeared upon the administration of orange-juice or other antiscorbutic food. In other words there is not only a rachitic beading but also a scorbutic beading. This conforms to the observation in experimental scurvy, as was noted in tests on guinea-pigs. In the same way but to a less extent in scurvy as well as in rickets there is seen the enlargement of the epiphyses. This is the probable reason of the confusion existing in regard to these two conditions, so that years ago scurvy was thought to be acute rickets. Beading of the ribs may also come about by lack of the water-soluble vitamin. It is of interest to note that beading of ribs has been observed postmortem in cases of infantile beriberi. As regards the influence of hygienic and non-dietetic measures on the development of rickets, it was found that rickets could develop in spite of an abundance of fresh

air. It was also found that a liberal allowance of light could not prevent the development of this disorder. Five children were given daily treatments with the violet ray. This treatment made no improvement on the rickets. The test diets were interesting from a point of view apart from the subject of rickets. In spite of the results of the experiments of others on rats, the authors failed to note similar results clinically. The only abnormal condition that they have noted has been a mild retardation in weight. Their experience led them to believe that under exceptional circumstances as in time of war, the danger to the infant from a deficiency of the fat-soluble factor is one not to cause great apprehension. It is not so widely distributed in nature as the water-soluble vitamin, but infants seem to be able to thrive for long periods on small quantities if the diet is otherwise complete. The great danger arises from diets composed merely of cereals and water or perhaps an insufficient amount of buttermilk or skimmed milk. There is a great danger of attributing to vitamins many little understood phenomena. They call attention to the peculiar and almost specific role played by cereal in the nutrition of infants. The gains produced could be recognized as due to an addition of any of the recognized vitamins, as diets rich in the fat-soluble, water-soluble vitamins, antiscorbutics, were improved by the addition of cereals. It was also not due to the simple increase of caloric value for the amount of food was comparatively insignificant. The simplest and most direct explanation of this is that this carbohydrate brings about a more complete oxidation and therefore a better utilization of the food.

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## OBSTETRICS

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UNDER THE CHARGE OF

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**The Care of the Pregnant and Nursing Woman.**—BOURET (*Arch. mens. d'obst.*, August, 1919) describes methods for caring for pregnant and parturient women in recently constructed maternities and under conditions in which much can be done to improve the health and vigor of the offspring. He believes that a modern maternity should include a portion devoted to the disorders of pregnancy, another in which labor and the puerperal period receive attention and an infirmary for abnormal cases, and in addition an out-patient or dispensary service. The portion allotted to the disorders of pregnancy may contain four rooms, in which are two beds each. The maternity portion for labor and the puerperal period should have twenty beds, of which six are in isolated rooms; twelve in two wards containing six beds each and two beds in a large room with an incubator for infants. The infirmary should have a dozen beds, six in rooms of one or two beds each for infected cases and six for aseptic cases. The dispensary should be connected with the whole of

the maternity. The infirmary department and that devoted to labor should be independent and the infirmary should again be divided into two parts: one for septic and the other for aseptic cases. These should be separated. The infirmary should be of two parts: one for septic and the other for aseptic cases, completely separated, each with its sterilizing room and operating room. There should be independent entrances to this portion of the maternity, but it should be possible to communicate directly with the maternity. While we may condemn such a communication principle, practically it seems very necessary. The maternity proper, so-called, should contain not only beds for the lying-in patients, but rooms devoted to the care of infants and a pavilion for operations. The part reserved for operations is practically a small independent hospital, isolated in such a manner that if necessary one can readily exclude those from without. There should be a sterilizing room, with two large horizontal autoclaves, and not only should dressings be sterilized, but also bed-linen and the garments worn by patients in bed. There should also be two large reservoirs of sterilized water, apparatus for sterilizing instruments, appliances and room for ordinary labor, one for minor obstetrical operations and a large hall for clinics and operations. In each of the operating rooms there should be a copious supply of sterilized water, hot and cold. The sterilizing service of the infirmary should be completely independent of that in the maternity. It may be built on the same model, but it needs to be very much smaller. The writer adds illustrative cases showing the benefits for patients or the different functions of the maternity hospital.

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**Intra- and Extra-uterine Pregnancy.**—BISSELL (*Am. Jour. Obst.*, December, 1919) records the case of a woman, married four years, without children. She had one abortion three years previously. She was taken subsequently with the classical symptoms of ectopic gestation in the right tube. At operation there was a typical ruptured ectopic pregnancy in the right tube. The pelvic cavity was filled with blood-clots, but there was no active bleeding. The tube, ovary and clot were adherent to the uterus and pelvic floor and the ovary and the tube were removed. The left tube and the ovary were slightly adherent. The uterus was large and soft, apparently two months pregnant. The patient made an uninterrupted recovery, left the hospital and returned at the normal termination of pregnancy, when she was delivered of a female child, weighing four and three-fourths pounds. Mother and child made a good recovery. From the interval of time elapsing between the operation and childbirth the question arises as to whether this was not a case of twin pregnancy. Many operators are accustomed to dilate and curette the uterus before removing by abdominal section an ectopic pregnancy. Recent study, however, has shown that this is injurious and the majority of operators omit it.

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**An Early Ovum in Situ in the Act of Aborting.**—WILLIAMS (*Am. Jour. Obst.*, September, 1919) describes a rare and interesting case in which an impregnated ovum was in the act of aborting. The growth of the ovum was thirty-eight days after the end of the last period. The ovum was already abnormal and shows the youngest stage of hydatid mole which the writer has yet seen. The specimen was contained in a

uterus removed by supravaginal amputation from a patient, aged thirty-nine years, married seventeen years, with three children. She had had eclampsia and phlebitis, then double femoral phlebitis, removal of the thyroid and repeated and prolonged attacks of mental depression. When first seen examination showed the uterus the size of a three months' pregnancy, but so firm and hard that a diagnosis of myoma was made. In view of the circumstances of the case it was decided after consultation to perform hysterectomy. This was done by the supravaginal method, retaining the normal tubes and ovaries. A typical corpus luteum was present in the left ovary. The patient's convalescence was uneventful, but her mental condition had not much improved. After suitable preparation serial sections were made of the specimen and thoroughly studied. No trace of the embryo could be found and the conditions were difficult to interpret. The decidua vera was thickest in the midline of the posterior wall. Section through the decidua showed the typical histological structure. The ovum was normal in location, and the only abnormality was the absence of fetal vessels and the parenchymatous stroma of the villi and the presence of large hemorrhagic areas scattered through the decidua outside the area of implantation. The ovum was evidently a very early one and abortion was in progress. One pole of the decidua capsularis had ruptured and the corresponding pole of the ovum was retarded through the defect.

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**The Pelvic Articulations during Pregnancy, Labor and Puerperal State.**—LYNCH (*Am. Jour. Obst.*, September, 1919) reviews the literature of the subject and states that sufficient examples of pelvic separation have been reported to excite interest in its mechanism. It is admitted that both the symphysis and sacro-iliac joints are lined with synovial membrane, and it has been shown that the sacrum normally rotates within small limits on the transverse diameter. The posture of the body is all-important in bringing about these different rotations. When the patient is squatting the promontory of the sacrum is shoved forward and the coccyx backward, thus increasing the diameter of the outlet. When the body is standing weight against the promontory pushes it backward, thus increasing the length of the conjugate vera. As the pelvic joints are softened in pregnancy the movements of the sacrum are increased. This condition consists in the phenomena of labor. Nature uses this condition to assist in fitting the fetus into the pelvis as a preparation for labor. Mercurio's position, afterward described by Walcher, is based upon the rotation upon the pelvic joints. In 500 cases the pelvis had been found more mobile than that of non-pregnant in all but 2 per cent. The separation of the pubis was not more than 3 mm., and only in 16 per cent. was it more than 1 mm. There were symptoms of the condition in 15 per cent. and in 70 per cent. there was change in the gait of the patient. The writer had used the roentgen ray and had studied these joint conditions, and also had an opportunity of observing a case of rupture of the symphysis during labor, the case coming under his observation three years after the rupture occurred. Litzenberg had found in 1000 cases 96 patients who needed treatment because of some abnormal condition of the sacro-iliac joints.

**Legislation Against Maternal and Infant Mortality.**—FOOTE (*Am. Jour. Obst.*, November, 1919) has gone over the laws enacted by different States to protect mothers and the offspring at the time of birth. The States differ very gently. The New York code is probably the most complete regulation for obstetric practice available. Some of the States attempt to define normal and abnormal cases. In regulating the practice of midwives States differ greatly in the minuteness with which the functions of the midwife are set forth. In several States the treatment of the newborn is described in detail. The majority of States require the registration of births and many exact the registration of the midwife. There is great difference in the standards of medical education to secure a license to practice for both physician and nurses. In some States a certificate of character is required, in some reference from an obstetrical school of recognition, while others conduct examination in various ways. Examination for license to practice include a considerable number of questions in obstetrics. Examination for license is frequently written and oral according with the wishes of the examiners. The penalty for violation of the laws pertaining to parturition differs greatly in different States, and in some fine and imprisonment may be imposed at the same time. Whenever midwives are kept and intelligently supervised the question of disinfection of clothing and equipment is included. Births must be reported in the majority of States within five days after the birth of the child. In summing up the whole situation it is found there is no uniformity of laws or even of required standards. Educational centers should be established to educate women in obstetric practice, whether as midwives, nurses, hospital officials or physicians. Community centers even in rural districts, should prove valuable. Supervisors, suitably compensated, and well-paid obstetrical visiting nurses should be employed as educators of midwives and of parturient women as well.

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**Extraperitoneal Tumor Complicating Pregnancy.**—VAN HOUSEN (*Surg., Gynec. and Obst.*, August, 1919) reports the case of a primipara, aged thirty-three years, who summoned her physician because she was suffering from severe pain. On examination a large mass was found in the posterior cul-de-sac about the size of a very large orange. It seemed to be an incarcerated tube. As the patient was not at the period of viability, she was kept in bed and given narcotics and placed in the knee-chest posture at frequent intervals. By this means she was carried along until the seventh month, when section was performed. On opening the abdomen the tumor was extraperitoneal. The abdomen was closed without performing section. An incision was then made in the posterior vaginal wall and the tumor was found feeling somewhat like a fibroid. While an effort was made to loosen the capsule the tumor was penetrated and was found smooth to the touch and filled with a bran-like tissue. This was freely evacuated, followed by severe hemorrhage, which was controlled by gauze packing. The gauze was removed on the fourth day. On the following day the patient expelled a male child through the vagina. This had been dead for a day or two because the external skin was separating. The mother did not have a high leukocyte count, nor at any time did she have a very low one. She died two weeks after the birth of the child. Ries studied this case and stated that the tumor



which he saw looked like a blood clot. On microscopic examination an enormous quantity of syncytial tissue was found. The gross appearance of the tissue resembled that of a blood-clot. The tumor was undoubtedly a syncytioma malignum.

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## GYNECOLOGY

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**Small Radium Dosage in Cancer.**—During the past two years SAMUEL (*Am. Jour. Roentgenology*, 1920, vii, 42) has limited his exposures to radium for malignancy of the uterus, to twelve hours, not using over 50 milligrams of the element, the dosage being 600 mg. hours for each treatment. His first year of radiotherapy was very disastrous during which time he used 150 mg. of the element for twelve hours and in a few cases for a longer time. Seeing the marked benefit from the smaller dosage, he thought larger doses and heavier screening would accomplish better results, but after seeing quite a number of fatalities which he felt sure were due to overdosage, he now makes the plea for *smaller* doses and at least a ten-day interval between exposures, filtering more at each exposure and stopping for four weeks at the end of the third exposure. He has been able to accomplish just as good results with this method as he did with the larger dosage, and with more comfort to the patient. The patients are not toxic after the smaller dosage, the bladder symptoms are eliminated and no proctitis is seen, all of which make the patient more miserable than does the growth. He generally gives three cycles of three treatments each with four weeks' rest after each cycle. At the end of three months, the treatments are resumed.

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**Trichomonas Vaginalis Vaginitis.**—A type of vaginitis due to the trichomonas vaginalis, an infusorial animalcule, has been described by DE LEE (*Illinois Med. Jour.*, 1920, xxxvii, 186), which is characterized clinically by obstinate vaginal discharge, pruritus, sleeplessness, burning and general weakness. The vulva and vagina are reddened and often rough like a nutmeg grater and sometimes minute hemorrhages are seen in the vaginal epithelium. The cervix is sometimes affected. The discharge is profuse, mucopurulent, thin, bubbly, acrid and has a disagreeable odor. Its irritating character is shown by the erosion of the skin, and especially in fat women there is an obstinate foul smelling intertrigo. Sometimes there are pointed condylomata similar to those

which are frequently present in cases of gonorrheal vaginitis. The diagnosis is easy. Even the clinical appearance of the vagina will suffice, but it is the work of but a moment to put some of the fresh discharge under the microscope and examine it, unstained, before it dries. The animalculæ are at once discovered by their active flagellation. The treatment that De Lee recommends is also very easy but it must be thoroughly done, preferably by the physician himself. The patient should be put to bed for two days. On the morning of the first day the vagina and vulva are scrubbed vigorously with tincture of green soap and water using a rough cloth and going most thoroughly into every fold and crevice. The soap is then rinsed out with sterile distilled water. This process is repeated three times and then a  $\frac{1}{1500}$  bichlorid douche is given with friction, every fold and crevice being washed. This is then washed out with sterile distilled water and the patient rests in bed. On the next morning the vagina is again washed out with green soap and water after which it is packed with cotton soaked with glycerine (4 parts) and sodium bicarbonate (1 part). The folds and crevices of the vagina are filled with the cotton and the vulva is smeared with the mixture. Next morning the tampon is removed and a sterile water douche is given. The following morning the secretion is examined under the microscope for trichomonas, but they are usually gone by this time. Only morning and afternoon douches of 2 per cent. soda solution are then given, but if the animalcules should return, the treatment should be repeated.

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**Rational Treatment of Uterine Cancer.**—After reviewing the statistical side of cancer of the uterus, both from the standpoint of operability and of curability, LITTLE (*Minnesota Med.*, 1920, iii, 159) concludes that the rational treatment of carcinoma of the body of the uterus consists of a panhysterectomy followed by prophylactic radiation with radium. In cervical carcinoma in the operable stage, either panhysterectomy followed by radiation or a thorough radiation without operation should be performed. From his present experience and observation, he is inclined to the belief that as good or better results can be obtained from radiation alone, with practically no danger or pain to the patient, radium penetrating beyond where the knife can be used. In inoperable cases, radium is much superior to any other treatment. Where there are large fungating masses producing toxemia, they should be removed with the cautery followed by radiation. He has abandoned the Percy cautery for radium and he does not advocate the Wertheim operation because of its high primary mortality, its serious sequelæ, such as vesical, ureteral and rectal fistulæ, and because there are too few cures to compensate the difficulties and dangers encountered.

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**Pulmonary Infarction Following Gynecological Operations.**—Several consecutive deaths from pulmonary embolism in the Gynecological Department of the Johns Hopkins Hospital aroused the interest of HAMPTON and WHARTON (*Bull. Johns Hopkins Hosp.*, 1920, xxxi, 95). They had been engaged in compiling their statistics but a short while when they made the observation that, in the case of many patients with phlebitis who later developed pulmonary complications, a diagnosis of pleurisy or pneumonia had been made without any reference to the

possibility of infarction. In their clinic the diagnosis of pulmonary infarction has been anything but good. They have recognized only 10 per cent of their cases, which they believe is due to the fact that the diagnosis has been based practically always upon the physical findings in the thorax instead of the whole clinical picture. The typical case of pulmonary infarction occurs in a postoperative patient who is convalescing from a laparotomy, frequently a hysterectomy. This complication occurs practically always in the second or third week after operation. The temperature curve is quite characteristic when not complicated by other factors. The patient has a low unexplained evening temperature of 99° to 100° F. after operation. After the day of the infarction the temperature rises sharply, but seldom goes much above 102° F. The curve is hectic in type, not like that of pneumonia. It reaches its highest point between the second and fourth days and usually drops almost to normal again at the end of a week. Infarction almost always makes its appearance in an acute attack with sharp sticking pain over the ribs as the dominant symptom. The attack may rarely be accompanied by a definite chill, although chilly sensations are rather frequent. The leukocyte count varies between 12,000 and 18,000 and is of little help in the diagnosis. The physical signs rarely make their appearance before the second day and the most constant of these is the friction rub, which was noted in 75 per cent. of their cases. They believe that it is probably present in a greater number, but this represents only those cases in which it was noted upon the history. Rales were heard in 75 per cent. of the cases; they are usually evident a little later than the friction rub. Impairment and changes in the breath sounds appear last and were noted in 63 per cent. of the cases. Pain ushers in the attack and is always the predominant symptom. Cough, while present in 63 per cent. of the cases at some time, is usually not severe, and in most cases is unproductive. Hemoptysis was present in 36 per cent. of the cases and when present, practically clinches the diagnosis. Phlebitis, pain and swelling of the leg occurred in 41 per cent. of this series, and when present is just as confirmatory as hemoptysis. In the typical case, the patient is out of bed, convalescing in a normal way when she is seized with a sharp pain in her side, more especially on deep inspiration. The nurse promptly returns her to bed and takes her temperature, finding it to be 100° F. the ward doctor is informed, makes a careful examination of the chest, but finds nothing definite. The patient is reassured and forgotten. On the following morning, in making his rounds, the doctor is informed that the patient still complains of pain in her side and that her temperature is 102° F. He goes over her chest promptly, finds a friction rub, with a few rales below the angle of the scapula and makes a diagnosis of dry pleurisy. A day or two later the patient may develop hemoptysis or phlebitis of the leg. She usually makes a prompt recovery and in ten days the little pulmonary upset is a thing of the past and forgotten. As a result of their extensive study on this subject, Hampton and Wharton conclude that postoperative venous phlebitis and thrombosis are not peculiar to any particular type of gynecological operations. There are a number of conditions that favor thrombus formation, but they believe that infection and trauma play the most important part. Phlebitis and thrombosis of the leg veins, when associated with pain

and swelling are rarely ever followed by fatal embolism. The important point brought out by this study is that postoperative pulmonary infarction in the majority of cases has heretofore been unrecognized chiefly because too much importance has been attached to negative physical findings and too little reliance placed upon a careful history.

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**The Relation of Pregnancy and Reproduction to Tumor Growth.**—While somewhat diverse views have been expressed concerning the influences exerted by pregnancy on tumor growth, the consensus of opinion seems to be that during pregnancy the proliferation of the new-growth is retarded. Obviously experimental animals in which spontaneous tumors develop offer the most favorable opportunity for the exact analysis of the subject. *SLYE* (*Jour. Cancer Res.*, 1920, v, 25) studied the rate of growth of an alveolar tubular carcinoma of the mammary gland in sixty female mice during their reproductive and non-reproductive periods. All of the animals had previously born young. In thirty of these after the tumor appeared no young were again born and tumor growth in these was compared with that of the remaining thirty, in which young were constantly born after the appearance of tumor. The results tabulated demonstrate in a very striking manner the influence of pregnancy in modifying the rate of growth in the coexistent tumor. The amount of tumor grown by the non-reproducing animals was much greater than that grown by the reproducing animals, the daily rate in the former being much in excess of that in the latter. Tumorous mice which are not bred live from four to six weeks after the appearance of the tumor, which proliferates with great rapidity, while the reproductive animals live from eight months to a year, during which time the tumor becomes almost quiescent. The number of the young borne appears to be a factor in retarding the rate of growth. When the mice cease reproducing the tumors commence to grow again with renewed rapidity and the female only survives six to eight weeks after the birth of the last litter. It was also observed that multiple tumors were more frequent in non-reproducing than in reproducing animals.

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**The Relation of Inbreeding to Tumor Production.**—Since inbreeding does not characterize the human race, any exact and comprehensive data concerning the relation of inbreeding to the incidence and inheritability of tumors must necessarily be derived from experimental animals. *Slye* has previously demonstrated that cancer inheritance in mice follows Mendelian ratios. These results were obtained by selected

mating. Similarly it is only by selected inbreeding that any increase in the numbers of tumors in a strain can be produced. Thus, SLYE (*Jour. Cancer Res.*, 1920, v, 53), by selected inbreeding (mating brother and sister of a hybrid strain carrying a definite percentage of cancer) in three branches obtained new strains with widely varying cancer incidence. One branch gave a tumor-free line, a second yielded a heterozygous line (*i. e.*, mice not themselves developing cancer but carrying it potentially) while the third was an extracted tumorous line. Since the progenitors of each line were brothers and sisters, and they were bred in the same manner, inbreeding, *per se*, was obviously not a factor in occasioning an increase in cancer. "What is put into a mating, and not the manner of putting it in, determines what characters shall appear in the offspring." It was shown that inbreeding, by lowering the vitality and diminishing the fertility of a strain, could eliminate cancer by racial extermination. It is important, in the analysis of results on the incidence of cancer, either spontaneous or inoculated, to bear in mind that the lowering of the vitality of a strain through inbreeding as well as by the hybridizing of stock which gives rise to inferior and infertile strains tends to decrease the percentage of cancer within the strain. The author maintains that "in the demonstration of the inheritability of cancer and other tumor types in mice their inheritability for man and every other species in which they occur has also been demonstrated." Further, since cancer and non-cancer tendencies segregate out and are transmitted as such in hybrid crosses, cancer being a recessive, can be eliminated from the human race, where the matings are hybridizations, by selected mating.

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**Varieties of Streptococci with Special Reference to Constancy.**—CLAWSON (*Jour. Infect. Dis.*, 1920, xxvi, 93) in a study of strains of streptococci isolated from various sources, paid particular attention to the constancy of the special characteristics, such as peculiarities of morphology, action on the blood-agar plate, fermentation of various carbohydrates, agglutination and complement-fixation reactions, in an attempt to discover whether the various classes adopted by previous workers have sufficient relationship to source, habits, pathogenesis or other particular characteristic to justify such grouping. From the author's investigations there seems to be no direct relationship between the length of chains and pathogenesis in streptococci. Capsules were found less commonly among hemolyzers than among non-hemolyzers. Of the 134 strains, hemolysis was constant after nearly two years of artificial cultivation, only 4 regularly failed to ferment lactose, only 2 always fermented mannit and only 3 always failed to ferment salicin. Evidence pointed to the fact that all non-hemolytic strains were methemoglobin producers when grown on suitable mediums, and of 150 non-hemolytic strains investigated, only 5 always failed to ferment lactose, 36 always fermented mannit and 75 always fermented salicin, there seeming to be more uniformity of fermentation among hemolytic than non-hemolytic streptococci. The regular type of fermentation placed most of the non-hemolytics in the class of *S. mitis* and *S. salivarius* (Holman). Considering the lack of relationship between fermentation reactions and source or pathogenesis, and the wide distribution of organisms falling into non-hemolytic groups, the author believes it is

doubtful whether any of the smaller groups of non-hemolytic streptococci deserve a place in classification. He also prefers the term *S. hemolyticus* to *S. pyogenes* and *S. viridans* to *S. buccalis* (Blake). It was further found that agglutination reaction between hemolytic organism and homologous serum showed a high degree of uniformity, while the reactions of hemolytic serum with non-hemolytic organisms, non-hemolytic serum with hemolytic organisms or non-hemolytic serum with non-hemolytic organisms, except the homologous strains, gave a low percentage of positive results. The reaction of hemolytic serum with hemolytic antigen yielded a higher percentage of complement-fixation than those of hemolytic serum with non-hemolytic antigen, or non-hemolytic serum with non-hemolytic antigen, or non-hemolytic serum with hemolytic antigen. From these observations it is concluded that the hemolytic group is a homogeneous group in which there is a relatively high degree of constancy and that the non-hemolytic group is heterogeneous or less homogeneous than the hemolytic group.

#### Observations on Paratyphoid Bacilli Recently Isolated from Animals.

—In a recent study of the tissues of several hundred swine which died of enteric diseases, SPRAY (*Jour. Infect. Dis.*, 1920, xxvi, 340) found the predominating bacterial flora to be members of the paratyphoid-enteritis group. The materials for study were obtained either from diarrheal swine by routine inoculations from heart blood, lung, liver and spleen, kidney and mesenteric glands, or from hog cholera virus by directly plating or inoculating the virus blood into rabbits. In the case of diarrheal swine the identity of all paratyphoid strains isolated from the various organs of the same carcass was not to be assumed, because in at least three instances, two or even three distinct strains were isolated from the same body. With few exceptions the strains were readily classified. Forty strains were studied in detail by the employment of arabinose, xylose, dulcitol, inositol, lead acetate agar, glucose serum water and agglutination and absorption tests; 23 of the forty strains were recovered from the tissues of diseased swine; 8 from hog cholera virus blood by plating and 9 from rabbits dying after inoculation with virus blood known to contain gas-producing bacteria. It was found that 34 of the 40 strains so studied were *B. suis*, 2 were identical with human *B. paratyphosus* A, 2 with human *B. paratyphosus* B and 2 were intermediate between *B. suis* and *B. paratyphosus* B. *B. enteritidis* was not encountered at any time. No true representative of the paratyphoid enteritis group was isolated from the feces nor from the lumen of the intestines. The author emphasizes this as he does the value of the selective cultural media mentioned above.

#### The Comparative Oxygen Avidity of Normal and Malignant Cells Measured by Their Reducing Powers of Methylene Blue.

—An interesting comparison of the reducing power of normal tissue and that of tumors is made by DREW (*British Jour. Exper. Path.*, 1920, i, 115) by means of methylene blue. A measured quantity (0.3 to 0.5 c.c.) of minced tissue was placed in a tube to which was added a definite amount of 0.001 per cent. methylene blue in Locke's solution minus the glucose. In order to prevent reoxidation a layer of paraffin was poured over each tube, which was then incubated at 37° C. During incubation the methylene blue became reduced to methylene white

by the tissue. The reduction commenced in the layer of the solution next the tissue and gradually extended upward in the column of colored fluid. While slight variations in the rate at which the reduction proceeded upward in each tube occurred with individual tissues, a very marked difference was observed between the tubes containing normal and tumor tissue. When the reduction rate was represented by means of a graph, two types of curves, which differed widely from one another, were obtained. In normal tissue the maximum reduction occurred in the first hour and gradually decreased in rate until the fourth hour, when the minimum was reached. The tumor tissues used were mouse carcinoma, mouse sarcoma, rat sarcoma and mammary carcinoma from a human subject. The reduction produced by tissues of these tumors showed a minimum during the first three hours and a small increase in the fourth and fifth hour, when it finally ceased. The only exception among the tumors was a neoplasm containing a considerable quantity of glycogen. In this case the curve tended to approximate that found in normal tissue. The curves obtained with methylene blue could be duplicated when hemoglobin was substituted for the dye, and the author concludes that the difference between the two types of curves is to be explained by the fact that the tumor cells have a lower oxygen avidity than the normal cells.

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**The Human Fecal Streptococci.**—Frequent and fragmentary allusions to the occurrence of streptococci in the gastro-intestinal tract have appeared in the literature. Most studies have had to do with the cause of specific diseases and consequently have presented difficulties of evaluation, often tending to complicate rather than simplify the situation. In an attempt to establish the normal streptococcal flora of the alimentary canal in accordance with the recent methods of classification, OPPENHEIM (*Jour. Infect. Dis.*, 1920, xxvi, 117) examined 55 apparently normal stools from fifteen healthy persons from which 323 strains of streptococci were isolated. The number of samples from any one individual varied from 1 to 5 and the number of strains isolated ranged from 11 to 49. The usual number of samples from one person was 4 and the average number of strains from these 4 was approximately twenty. The method of culture consisted in diluting a few loops of feces in sterile salt solution and streaking the surface of a 10 per cent. sheep blood-agar plate. After eighteen to twenty-four hours' incubation at 37° C. colonies were fished to glucose broth and reincubated. Replatings were made from the broth and the colonies picked to blood-agar slants, from which the carbohydrate media were seeded and read in five days. Meat infusion broth, pH. 7.5, was employed. The carbohydrate medium was 1 per cent. except salicin (0.5 per cent.), and bromocresol purple served as the indicator. Hemolytic and "indifferent" varieties of streptococci were rarely found. The green-producing strains were most frequently encountered, and of these all fermented glucose, 8 failed to ferment lactose, 9 failed to ferment salicin and 4 failed to ferment mannit. According to Holman's classification, *S. fecalis* occurred in 73 per cent., *S. salivarius* in 1 per cent., *S. non-hemolyticus* I in 23 per cent., *S. equinus* and *S. ignavus* in 1.5 per cent. Mannit fermentation, though the most important fermentative characteristic, was found to be quantitatively less uniform than that of

other carbohydrates. No apparent morphologic characteristics aside from those dependent on rapid, luxurious growth, characterized the strains isolated.

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## HYGIENE AND PUBLIC HEALTH

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**A Study of the Relation of Diet to Pellagra Incidence in Seven Textile-mill Communities of South Carolina in 1916.**—GOLDBERGER, WHEELER and SYDENSTRICKER (*Public Health Reports*, 1920, xxxv, 648) set out to determine the explanation for the outstanding fact, observed many years ago, that poor diet was associated with pellagra. Goldberger had earlier called attention to the significance of the fact that nurses and attendants, at institutions where pellagra was rife, appeared to be immune. A study of the conditions showed that the apparently immune used a diet containing less cereal and vegetable components, and more fresh meats, eggs and milk. Experimental studies clearly showed that when the diet of inmates was supplemented so as to contain a larger proportion of animal protein foods the disease disappeared. In one institution the diet of certain patients was supplemented in the manner indicated, while that of others was not changed, with results that clearly proved the prophylactic benefit of the more liberal diet. By feeding a faulty diet to volunteer convicts it was possible to induce pellagra among those, while ten other prisoners remained free. In the present study accurate observations were made on the diet used by pellagrous and non-pellagrous families and on the economic and sanitary circumstances. Special stress was laid on the necessity for data on dietary conditions in the months prior to the annual appearance of pellagra which reaches its height in June. The seven villages were typical cotton-mill communities ranging in population from 500 to 800 inhabitants, practically all of native-born Anglo-Saxon stock. House-to-house visits were made for the purpose of discovering cases that otherwise would have escaped observation; in addition, cases were reported by physicians, though apparently but a small percentage of cases came under medical care. Only cases with a clearly defined eruption were counted as pellagra, though the authors believe that by adhering to this criterion some cases were excluded. The data for basis of the dietary studies were based on records of the purchases or production of food consumed by a household. The outstanding difference between pellagrous households and others lay in the more liberal supply of foods of the animal protein group in the latter. Just what component of these foods is essential in the prevention of pellagra remains to be determined. The results of the study give no support to the theory that



the eating of corn is associated with the development of pellagra. The availability of a more abundant supply of fresh milk and fresh meats is regarded as the most important factor in the prevention of pellagra.

**The Diagnosis of Helminthic Diseases of Man.**—HICKEY, (*U. S. Public Health Reports*, No. 24, 35, 1383) reports on the examination of oriental immigrants at the U. S. Immigration Station, San Francisco, California. The technic employed is as follows: (1) A piece of (preferably) formed stool, approximately the size of a walnut, is placed in a porcelain cup, and after taking about 60 c.c. of cold water, the mass is thoroughly disintegrated with the aid of a wooden tongue depressor. When disintegration of the feces is as complete as possible the tongue depressor is destroyed. If the stool is liquid an equal bulk of cold water is added and mixed as indicated above. (2) After placing over the mouth of the cup two or three layers of wide-mesh surgical gauze, a portion of the contents of the cup is strained into a tube and centrifugalized for ten seconds at 1500 to 2000 r. p. m. The gauze is thrown away and a new piece used for the next specimen. The cup is emptied of its remaining contents and thoroughly scalded. (3) The tube is removed from the centrifuge, and, without disturbing the sediment, the supernatant liquid is poured off and the tube refilled with cold water to about three fourths its capacity. (4) A thoroughly clean rubber pad is placed over the mouth of the tube and held in place by the thumb while the tube is shaken vigorously. When preparing two tubes at the same time extreme care should be taken to use the rubber pads on their respective tubes at each shaking. (5) The contents are again centrifugalized for ten seconds. (6) The supernatant fluid is poured off as described above, the tube is refilled with cold water and again shaken. (7) Centrifugalized again for ten seconds. (8) The supernatant fluid is poured off, leaving about  $\frac{1}{2}$  inch overlying the undisturbed sediment. The specimen is now ready for microscopic examination. (9) A smaller amount of the sediment is placed on a slide, and sufficient water is added to almost completely cover it. This is mixed with the aid of a toothpick or match and allowed to stand for two or three minutes; the excess fluid is poured off onto another slide, more water is added and this is allowed to stand while the first slide is being examined microscopically. This procedure can be repeated with a third slide, though usually the second will suffice. It often happens that ova will be found on the second slide and not on the first, on account of the lower density of the former, which permits the ova to settle more readily. With respect to clinical aspects, eosinophilia should always excite suspicion. Anemia may or may not be present and other symptoms may be wanting, even in heavy infestations. The ova of the various parasites, trematodes, cestodes and nematodes are described in detail.

**Statistics of Influenza Morbidity.**—FROST (*Public Health Reports*, 1920, xxv, 584) discusses the data collected by canvasses made in 40 cities ranging in population from 25,000 to 600,000 and smaller communities. Five thousand or more persons were canvassed in each locality. The rate of attack in various communities varied from 185 per 1000 to 535 per 1000; this was without special relation to geographic location or size. The attack rate was highest in the age group 5 to 9 and declined with increasing age, except for the groups 25 to 34, in

which the incidence was higher than in the group 15 to 24. Almost uniformly the rate was higher for women than men and lower for the negro race than for the white. The latter is surprising in view of the normally high incidence of respiratory infections among negroes. The case fatality varied from 3.1 per cent. to 0.8 per cent., being generally higher on the North Atlantic seaboard and the Pacific Coast. The case fatalities differed for different age groups and was generally higher among negroes than among whites.

**The Experimental Production of Pneumonia with the Influenza Bacillus of Pfeiffer.**—MAJOR (*Jour. Med. Research*, 1920, xli, 373) states that the results of the experiments undertaken in his study indicate that the invasive powers of *B. influenzae* are limited. When the organisms are injected intravenously the effects produced are to be explained by a toxic action rather than any direct bacterial action produced by multiplication and spread through the blood stream. In no cases were the bacilli recovered from the blood cultures in animals which had been injected intravenously with influenza bacilli. Introduction of *B. influenzae* into the trachea was successful in producing bronchopneumonia. In these cases, also, the invasive properties of the organisms were apparently limited, as the bronchopneumonic patches were small, few in number and confined to the hilus of the lungs. The location of these areas also suggested a local direct action of the masses of bacteria, with but little extension to other portions of the lungs. In contrast to the results obtained by the intravenous and intratracheal introduction of the bacilli a preliminary irritation of the respiratory tract with chlorin gas permitted an extensive invasion with influenza bacilli injected intravenously or intratracheally. The pathological changes produced in the lungs were striking and intense in degree and resembled the lungs in fatal cases of human influenza. In the majority of these cases influenza bacilli were grown from the lungs in pure culture.

**Tellurium as a Health Hazard in Industry.**—SHIE and DEEDS, (*Public Health Reports*, No. 16, 35, 939) present evidence on the importance of tellurium as an industrial poison. The element tellurium resembles metals physically, but chemically is related to sulphur and selenium. It is used in the production of colored glass. The cases of poisoning in question were among employees of a silver refinery and were men who were exposed to fumes and dust containing the poison. The main channels of entry are by the respiratory and alimentary tracts, but the skin probably absorbs some. In the body this poison becomes converted into a compound which imparts a garlic-like odor to secretions and excretions. The poison is eliminated through feces, urine, lungs and skin. The symptoms are summed up as follows: "Garlic odor to the breath, sweat, and alvine discharges, dryness of mouth, metallic taste, nausea, anorexia, loss of weight, constipation or diarrhea, suppression of the sweat, and a dry, itching skin. Associated with these symptoms are likely to be a hypoacidity of the gastric juice, with a mild gastro-enteritis and parenchymatous nephritis. Inasmuch as the symptoms of mild tellurism are the same for man and the laboratory animals, we have reason to believe that the more severe effects, as well as the pathological changes, would likewise be similar. As yet

we have met with no severe cases of tellurium poisoning; but we should expect such cases to exhibit violent vomiting, purging, intestinal hemorrhages, loss of reflexes, tremors, extreme depression, and finally paralysis of the central nervous system, with unconsciousness, dyspnea, and at last death in convulsions. Associated with these symptoms there would be destruction of the red blood cells, decreased hemoglobin content, hemorrhages into the various organs, and a severe gastro-enteritis and nephritis." The hazard seems to be high, as more than half of the men exposed to the fumes showed evidence of poisoning. The prevention lies in the observance of precautions applicable to other metallic poisoning, such as adequate ventilation, use of respirators, proper washing and drinking facilities. Full coöperation on the part of the employee is necessary. The prognosis is good, and treatment consists of eliminative and supportive measures.

**Recent Work on Pellagra.**—VOEGTLIN (*Public Health Reports*, No. 25, 35, 1435) reviews the history of pellagra and refers especially to the limited geographical distribution. Attention is called to the fact that clinical observers long ago laid the foundation for the latter-day research that has been so fruitful, as follows: "Thus Casal, Strambio and others speak of the good results obtained with a mixed diet. Roussel, in his admirable *Traité de la Pellagre*, states that the real treatment of pellagra is a milk diet, and supports this statement by the histories of a number of cases which were evidently cured by a liberal diet. Lussana and Frua (1856), on the basis of over 8000 cases treated with a liberal mixed diet, claim that the mortality fell from 24.5 to 4.5 per cent., and that the recovery rate increased from 20 to 75 per cent. as a result of this treatment. The value of the dietary treatment was therefore well established and almost universally accepted even by the adherents of the infectious and "spoiled-corn" theories. This was a most significant fact, which gained in importance when it was brought into relation with the characteristics of the diet consumed by persons prior to their attack of pellagra. The striking features of this diet appeared to be its lack in certain animal foods, such as milk and meat and eggs, the same foods which proved to be so beneficial in the treatment of the disease." Attempts at producing the disease in animals are described as well as studies of metabolism. The evidence of the dietary deficiency that is responsible for the disease is fully described. Vitamine deficiency is less likely than "that the pellagrous syndrome is caused by a combination of the deficiencies in some of the well-recognized food factors, a hypothesis which would account, first, for the resemblance between the symptomatology and histopathology of scurvy, beriberi, and pellagra, and, second, for the great individual variation in the symptom complex observed in different patients. The precise nature of the dietary deficiency remains to be discovered.

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ORIGINAL ARTICLES.

DIAGNOSIS OF GALL-BLADDER DISEASE.

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THIS paper is based upon experience derived from two sources: (1) from work for twenty years past in medical wards, and (2) from private practice for the same period in internal medicine. But the records of patients seen in wards have been accumulated by various observers, including interns, students and laboratory workers, and, furthermore, are not available now for study; they are therefore excluded from consideration, except as they have influenced the formation of opinions here expressed. All records made in private practice to April, 1906, were destroyed in the fire that swept San Francisco then. During the following thirteen years, from January, 1907, to January, 1920, there were seen for diagnosis and advice 6180 different patients, all of whose records have been preserved. But because the earlier ones of these are not as complete and detailed as the later, only the records for the past eight years have been reviewed as a basis for this study. During this period the total number of patients seen has been 3513, and among these there have been 114 where the diagnosis made was gall-bladder disease.

The methods employed to reach this diagnosis have been the usual ones of history, physical examination, laboratory and roentgen-ray investigations.

I. History. The value of this is so great, especially in all digestive disturbances, that no amount of time spent in eliciting it is ever

wasted. In all these records the history has been taken personally, not through assistants; has been written out in detail, often in the patient's own words; has been revised and supplemented at succeeding interviews, as the case progressed; and has certainly played the most important part in solving the problems presented. But there are numerous variations in the story told by the patient with gall-bladder disease and no one account fits every case. There seem to be four distinct groups, according to history, as follows: *Group 1.* Recurring attacks of colic, with good health between. *Group 2.* Recurring attacks of colic, with more or less constant indigestion between. *Group 3.* Chronic stomach trouble, with subacute gall-bladder attacks. *Group 4.* Chronic stomach trouble, with no history whatever pointing to gall-bladder over long periods of time.

*GROUP 1.* These are the patients with attacks of biliary colic recurring at irregular intervals, with good health for months or years between. The description they give is usually so characteristic that the story by itself makes the diagnosis. The sudden onset without known cause, the violence of the pain, its site at the right costal margin, its radiation under the right shoulder-blade, its duration for hours at least, all combine to make a picture that is unmistakable. Such a history as the following is typical of this group:

A woman, aged fifty-one years, complains that for the past five years she has had recurring attacks of pain in the upper abdomen. These may come once a month or even once a week, but she has gone two or three months without one. In the interval between attacks she feels perfectly well. The pain comes and ends very suddenly; is felt in the pit of the stomach and across the upper abdomen, radiating to the back, under the right shoulder-blade; its character is colicky and griping; its intensity is very great at times but not always equally so; its duration is very variable but never less than two hours. The attacks bear no relation to food and may precede or follow a meal. During the pain she is nauseated but rarely vomits. After one severe attack distinct jaundice followed. At operation this patient had a small contracted gall-bladder, containing two large stones which completely filled it.

Certain variations of this typical picture may, however, mislead. For instance, the pain may be situated in the epigastrium and radiate straight through to the back, leading to an indefinite diagnosis of indigestion or gastralgia; it may radiate to the left side rather than to the right and so create a suspicion about the heart; it may radiate upward beneath the sternum and thus closely simulate angina pectoris; or it may radiate downward along the right side of the abdomen and so point to the appendix as the site of disease. As regards jaundice, its occurrence as a sequel to the attack of colic makes gall-bladder disease practically a certainty; but its absence

from the story does not throw doubt on the diagnosis when other details are characteristic. Many attacks at their height are accompanied by vomiting, after which the pain subsides; so that the patient is convinced the stomach caused the attack, and this error may be shared by the physician unless he takes into consideration all other parts of the story. But these minor variations in radiation of pain and the presence or absence of jaundice, accompanying stomach symptoms, are all insignificant in comparison with the main features of sudden onset, severity of suffering, site of the pain, repetition of attacks after an interval of good health, and their occurrence unexpectedly, night or day, with no recognizable cause. This history is the most frequent of all in gall-bladder disease, and in this group 45 cases have been recorded out of the total of 114 diagnoses made.

GROUP 2. This group presents not only the story of these recurring attacks of colic but also a complaint of constant stomach trouble between. In fact, the suffering caused by indigestion so obsesses the patient that not infrequently the paroxysms of pain are forgotten in the history unless direct inquiry is made about them. Their features are the same when described as in the cases in Group 1, and the only difference lies in the distressing dyspepsia that fills the intervals between. The following case history is typical of Group 2.

A woman, aged fifty-nine years, complains of spells of what she calls "indigestion" ever since she was twenty: at first coming years apart, but gradually more often, so that now they recur every few months. These spells are characterized by very severe pain, always requiring morphin for relief. This pain comes on gradually and gets worse and worse; is felt in the pit of the stomach, running through to the back; is steady and continuous, not colicky; not accompanied by nausea or vomiting; lasting for hours or until morphin is given; and frequently followed by jaundice for a day or two. In addition to this story she has another of constant trouble with her stomach for twelve years past. She retains her food about three hours, then distress comes on, her stomach grows sour and she has to vomit to get relief because nothing else will give it. She feels better at once after eating, but about two or three hours later her stomach feels too full and burns so that she drinks soda and warm water until she vomits. This condition goes on regularly every day and after every meal and has done so for twelve years. This woman at operation was found to have a small thickened gall-bladder containing one large stone and many small ones.

The manifestations of stomach disturbance are not always the same in gall-bladder disease. Many times the story told corresponds closely to that we are accustomed to attribute to gastric ulcer, because the symptoms are really due to hyperacidity: heartburn,

water-brash, belching, pain, nausea, vomiting, coming on regularly an hour or two after meals. But in other cases the story resembles that found in chronic gastritis and due to hypo-acidity; distress, fulness, sense of weight and distention occurring soon after eating, with persistent belching of gas. The relative frequency of these two varieties of dyspepsia produced by gall-bladder disease will be considered later, when we come to discuss what stomach contents show after a test-meal. But there is nothing about the patient's description of his stomach trouble to identify the gall-bladder as the cause. The evidence that does fix the blame is furnished by the intercurrent attacks of biliary colic, similar in all respects to those described in Group 1. There were 25 cases seen during the past eight years whose history corresponded to the one given in detail for this group.

GROUP 3. The history here varies from both the preceding in that there are no attacks of violent pain. The chief complaint again is of the stomach, and indigestion makes up the main part of the patient's story. But, in addition there is given, or can be elicited by questioning, the account of another kind of annoyance or suffering, not so constant but recurring from time to time in "spells." Sometimes the symptoms in these spells amount only to discomfort; sometimes they are more severe; but they never approach in severity or character the typical biliary colic. The location of these manifestations, which the patient recognizes as different from the constant stomach distress, is usually the right side under the ribs, where there is a feeling of fulness and soreness and of something in the way. The following case history presents the story usually told by patients in this group.

A woman, aged sixty years, first seen in January, 1915, complains of stomach trouble she has had for years, characterized by a heavy aching that comes on two or three hours after eating, persisting often until the next meal, with much belching of gas. Her bowels are never constipated but she suffers frequently from diarrhea. The stomach symptoms are nearly constant, the attacks of looseness of the bowels last for several days in every month. Besides these disturbances of health, she describes still other attacks, characterized by dull, aching pain, or "a hurting," as she expresses it, in her right side for days at a time, particularly after getting very tired or after taking a long ride. This pain is never sharp or severe, always dull, aching, annoying and nagging. This patient was found to have complete achylia; was dieted and treated medically at intervals without much benefit; until finally, in April, 1919, she had for the first time in her life an attack of very violent pain, typical of biliary colic, followed by jaundice. She then consented to the operation repeatedly advised during the preceding four years, and was found to have a gall-bladder, with walls greatly thickened and very tough, containing one large round stone.

Other patients in this group tell of a feeling in the right side as if there was "a sore ball" there; of a beating and throbbing and tenderness; or as if something there was going to break because of the sense of fulness; or as if there was something in the way when they bend forward or when they raise the right arm. These symptoms come only at intervals, lasting usually for a day or a few days; but the stomach symptoms are practically constant. The latter are not always the same and there is nothing characteristic about them to identify them as due to gall-bladder disease. This condition is not an unusual one, for there were 34 patients who presented the typical story that placed them in this group.

GROUP 4. There remain certain patients that complain much of the stomach over long periods of time, with no explanation to be found in their history as to the real cause. Sometimes the symptoms they describe correspond to the so-called gastric ulcer type; sometimes to the so-called chronic gastritis type; sometimes a story of gradual loss of weight, in connection with that of chronic dyspepsia, causes suspicion of cancer of the stomach. Frequently in former days these patients were set down as suffering from a "gastric neurosis;" and not infrequently even to this day some of them are labelled with a diagnosis of "achylia gastrica." There are no attacks of biliary colic to direct attention to the gall-bladder, and not even the less serious discomforts described in Group 3. There is really no way to be sure that these cases are due to gall-bladder disease until suddenly, sooner or later, perhaps after the lapse of years, comes a typical attack of severe pain like that described in Groups 1 and 2 to settle the matter definitely; or until, in despair, after trying repeated dietetic and medicinal methods of treatment, without benefit, the patient submits to exploratory operation. That such cases exist, any clinician of experience comes gradually to realize; and though over long periods we cannot reach certainty by any method of diagnosis, we learn to suspect the existence of gall-bladder disease in certain types of history, even though no definite proof is furnished by other methods of investigation. To this group ten cases have been assigned during the past eight years. Others perhaps exist in these records that have been classified under some other name than gall-bladder disease, and that will ultimately reach their proper diagnostic group as development bring out their true nature. A brief *résumé* of the story of several of the cases placed in Group 4 will best show the difficulties of the diagnostic problem.

CASE I.—A man, aged fifty-three years, complains of stomach trouble for about four or five months. He has no appetite and fears to eat because all food causes a feeling of fulness and oppression soon after eating, even while eating. He belches much gas, but has no pain or nausea or heartburn. He has lost twenty pounds since his illness began. His stomach analysis shows complete achylia. Continuing to lose steadily in weight and improving in no respect



on diet and digestive aids, he finally submits to exploratory operation, when the only pathology found is a large single gall-stone, completely filling the gall-bladder. After its removal his symptoms all disappear.

CASE II.—A man, aged forty-two years, first seen in April, 1915, complains of indigestion off and on for the preceding three years. When this occurs he loses his appetite, food causes distress soon after it is taken, he feels too full and distended and belches much gas. He has no nausea or vomiting. He has lost in weight and strength and become very nervous. His stomach also shows complete achylia. The indigestion subsequently continues at intervals in spite of medical treatment, though never sufficient to incapacitate him, until finally, after a Thanksgiving dinner in 1919, he has for the first time after eight years of "stomach trouble" an attack of very severe pain in the upper abdomen, lasting for many hours, with persistent vomiting and followed by jaundice. After this he himself discovers a lump in the upper abdomen the size of a turkey egg, and operation shows a large gall-bladder distended by mucus, the cystic duct blocked by a large stone and many other stones free in the gall-bladder.

CASE III.—A woman, aged thirty-eight years, seen first in February, 1911, complains that she is nauseated nearly all the time, bloats after eating, her food causes heartburn, belching and much gas, but she has no pain and never vomits. She is set down at that time as a case of gastric neurosis, and continues to have more or less similar trouble with her stomach for nearly six years following. Then in December, 1916, begin a series of attacks of very severe pain in the pit of the stomach through to the back, with nausea and vomiting, lasting until morphin is given. Finally, operation in February, 1917, revealed a contracted gall-bladder with thickened walls, containing one large stone.

CASE IV.—A man, aged sixty-two years, complains of stomach trouble present for six months previous. At the outset this was not constant, but lately the stomach never seems right. The appetite is poor and food causes distress, coming on several hours after eating. There is no severe pain every day, but at times it is so severe he cannot sleep, its recurrence depending apparently on what he eats, though any food causes more or less distress. There is much gas and belching. There is no nausea but when a severe spell comes he forces himself to vomit for relief. He has lost about twenty-seven pounds in weight since his illness began. Because of marked hyperacidity found by stomach analysis, and the evidence given by roentgen-ray plates, this man is thought to have duodenal ulcer. He is treated for this and after a month's routine his symptoms all disappear. He remains well for nearly a year, then the symptoms all recur; and this time, after two weeks of gastric disturbance, suddenly comes a typical attack of biliary colic followed by jaundice.

Operation showed the usual thickened and contracted gall-bladder containing two large stones.

Thus in Group 1 of gall-bladder histories, recurring attacks of biliary colic characterize the story, with good health between. In Group 2 stomach symptoms play a prominent part but the colic attacks still form the diagnostic feature. In Group 3 the stomach symptoms preponderate, colic has disappeared and the gall-bladder symptoms have quieted down to minor importance. In Group 4 there are no symptoms but those produced by the stomach, over months or years, and the gall-bladder speaks only vicariously, calling no attention directly to itself. There should really be a Group 5 described where the gall-bladder contains stones, but gives rise to no symptoms of any kind; until either some sudden violent attack of pain, or operation performed for some other ailment reveals cholelithiasis. But these cases sooner or later develop symptoms that put them into one of the four groups described, and they cannot be diagnosed until they do.

**II. Physical Examination.** In gall-bladder disease this method of diagnosis stands next in value to history, but even so the evidence it gives is very uncertain. The possible results are of three sorts: (1) entirely negative; (2) purely subjective; (3) definitely objective as well as subjective.

1. *Negative Findings.* To anyone who has witnessed operations on the gall-bladder and has noted how far this organ lies beneath the costal margin; furthermore, how small and shrunken the diseased organ is, no surprise is caused by the fact that physical examination so often gives negative results. Nothing abnormal can ordinarily be made out by palpation, during long periods when a diseased gall-bladder is quiescent, even though reflexly it is causing incessant gastric distress.

2. *Subjective Evidence.* Tenderness may be elicited by various manipulations beneath the costal margin, with the patient in different postures; but at the same time no change from the normal be conveyed to the examiner's fingers at all. What the patient feels and the diagnostician does not feel must always be considered with due allowance for individual susceptibilities.

3. *Objective Evidence.* Objective evidence found in gall-bladder disease is of two kinds: (a) increased tension and rigidity, and (b) palpable tumor.

(a) Increased resistance in the right hypochondrium as compared with the left, combined with tenderness on deep pressure there, is the sign we expect to find when cholecystitis is present. But this may not be discovered at one examination and found at another. It is much more likely to be elicited soon after an attack of biliary colic or during the periods of dull ache and sense of fulness described in Group 3. This definite abnormality is probably due to acute exacerbations of a chronic cholecystitis, and disappears again as

soon as the acute inflammation has subsided, so that its absence over long periods of time does not indicate the absence of gall-bladder disease, which may in fact be extensive and advanced.

(b) The discovery of a palpable tumor in the gall-bladder area may possibly mean nothing but chronic adhesions about the organ and gall-stones within it. But usually it means more—either an obstruction to the cystic duct with retention of bile or else a neoplasm. It is a law of clinical medicine, long ago announced by Courvoisier and since confirmed by many observers, that in chronic jaundice due to obstruction of the common duct by a gall-stone the gall-bladder is small, while in chronic jaundice due to neoplasm the gall-bladder is distended. This law is based upon the fact that chronic cholecystitis and cholelithiasis make the gall-bladder small, thickened and contracted; and if on physical examination a tumor is palpable with or without jaundice, the conclusion is therefore justified that something unusual has been added to the clinical picture, and that there exists distention of the gall-bladder by accumulation of bile and mucus within its cavity or else neoplasm that has developed in its walls. But as these conditions are unusual so ordinarily no tumor is palpable in gall-bladder disease.

**III. Laboratory Examination.** No diagnostic evidence is furnished by blood counts in gall-bladder disease. The urine may be dark in color and show bile, while the feces are light in color and show deficient bile, during or shortly after an attack of biliary colic, even though the skin and conjunctivæ are not noticeably yellow. But urine and feces convey no information of diagnostic value in gall-bladder disease except at the time of such emergencies. As regards direct examination of bile obtained by duodenal tube, as described by Einhorn, Rehfuss, Lyon and others, attempts have been made in this series of cases to employ this method, but not with satisfactory results. The objections found have been with the practicability of the method not with its value; but this value has not been found so great as to offset the obstacles offered in securing duodenal contents and in getting them properly examined chemically, microscopically and biologically.

As regards stomach analysis, it tells us when abnormalities in secretion exist but nothing as to their cause; and there is no type of abnormality absolutely diagnostic of gall-bladder disease. In the series of cases reviewed, gastric analysis was made 81 times. With stomach contents removed forty-five minutes after the Ewald test-meal and assuming the normal range of total acidity to be 40 to 60, the results found were as follows: total acidity under forty in 26 cases and under twenty with complete absence of free HCl in 12 of these; total acidity over sixty in 38 cases; all the other seventeen analyses within normal limits. There were therefore more patients found with hyperacidity than with hypo-acidity in this series. From experience acquired not only in these gall-bladder cases but in many

other gastric disorders from which these have been sifted out the truth seems to be as follows: gall-bladder disease may be associated with either hyperacidity or hypo-acidity; but while hyperacidity is found as frequently with ulcer or chronic appendicitis as with gall-bladder disease, hypo-acidity, and particularly achylia, is found with gall-bladder disease more often than with any other pathology except cancer. Therefore the discovery of achylia with a dubious history of chronic stomach trouble, as in the cases in Group 4, adds much to the suspicion that disease of the gall-bladder is the underlying cause.

**IV. Fluoroscopy and Roentgen-ray Plates.** Much information of great value is supplied by this method of diagnosis in gall-bladder disease; nevertheless, it may in a given case add nothing to the facts already collected by other means, and, on the other hand, the testimony it gives may appear to implicate the gall-bladder when no disease is there. The evidence obtained by this method of investigation is of three kinds: direct, indirect and eliminative. (1) Direct evidence means the demonstration of changes in the gall-bladder itself, either the shadow of its outlines or of stones within it. But these findings are unfortunately not the rule even when other evidence is conclusive. A liberal estimate seems to be that one-half the cases of gall-bladder disease give such direct signs by means of the roentgen ray, and possibly this estimate should not be more than one-quarter. (2) By indirect evidence is meant demonstration of effects produced on other surrounding parts by the gall-bladder disease, such as flattening or deformity of the duodenal cap; pulling of the stomach to the right, or a high position and fixation of the hepatic flexure of the colon. But all of these signs are caused by pericholecystitis, leading to adhesions between the gall-bladder and adjacent organs, and as pericholecystitis does not always occur, even with long-standing gall-bladder disease, none of this indirect evidence may be found. (3) By eliminative evidence is meant the exclusion of other pathology possibly causing the history and physical signs and disturbances of stomach function. It greatly simplifies the diagnosis in certain cases to have positive demonstration by fluoroscope and by roentgen-ray plates that no cancer or ulcer exists at the pylorus or in the duodenum; that no changes are found to indicate disease about the appendix or cecum; that there is no break in the continuity of the colon and no marked ptosis of stomach or bowel. These negative findings are certainly of great value and justify the investigation even though no positive signs are found that point to gall-bladder disease.

But interpretation of what is shown by fluoroscope and by roentgen-ray plates is always open to error and must not be accepted as final when it disagrees with evidence obtained by other means. For instance, in several of the cases reviewed in this series, with

most positive history pointing to gall-bladder disease and with gall-stones subsequently found at operation, the roentgen-ray report was entirely negative, no direct or indirect evidence being furnished of the condition present. Again, with chronic gastric disturbance due to hyperchlorhydria as shown by gastric analysis, with no history pointing to gall-bladder disease, and with much depending on roentgen-ray examination to throw some light on the pathology present, the report comes back of a deformed duodenal cap leading to a diagnosis of ulcer. But ultimately an attack of biliary colic justifies a revision of this diagnosis, and at operation the deformity of the duodenum is proved to be due to adhesions. Great, therefore, as is the value of roentgen-ray evidence, it must be remembered that it is not infallible, and its testimony must not be accepted as unassailable.

Such are the methods by which we recognize the presence of gall-bladder disease. There are not many forms that this presents. Probably cholecystitis is always the first phase, and this must exist for a variable length of time before gall-stones are added and the condition becomes cholelithiasis. Theoretically we ought to be able to distinguish one from the other, but practically we are not; and, after all, it makes no great difference, for a diseased gall-bladder needs to be removed whether it does or does not contain stones. When a stone becomes lodged in the cystic duct and the gall-bladder consequently distended because its outlet is blocked, an elastic tumor forms that is easily palpable and usually can be recognized without difficulty. If a hard tumor is found instead, whether smooth or irregular, suspicion should be aroused at once of cancer. But here again differential diagnosis should not take up much time, because either condition calls for surgery as promptly as possible after a tumor is discovered. As it is difficult to decide where cholecystitis ends and cholelithiasis begins, so it is equally difficult to tell where cholelithiasis ends and cancer begins. We have no methods, unfortunately, for the recognition of malignant degeneration of the gall-bladder before a palpable tumor has formed, and then it is usually too late for the surgeon to successfully remove it, because of metastases.

In conclusion, history seems to be the most valuable aid in the recognition of gall-bladder disease. When this is characteristic, as in Groups 1 and 2, it makes the diagnosis, no matter whether or not at a given time signs are found by physical examination, no matter what the stomach analysis shows, no matter whether the roentgen-ray report does or does not present any direct or indirect evidence. When the history is less characteristic, as in Group 3, it still remains the most important factor in diagnosis; but physical examination comes next in value and may give signs that with the history serve to remove all doubt, regardless of laboratory and

roentgen-ray reports. When we come to Group 4 history alone makes us only suspect, and we need all the clues we can get from physical signs, secretory disturbances and roentgen-ray shadows to enable us to pass beyond suspicion that the gall-bladder is diseased. Without enough collateral evidence to supplement deficient history in this group we cannot reach certainty, and so we usually wait for months or years, indefinite and undecided, until at last it is history that settles the matter by introducing an attack of biliary colic. Thus we come back in the diagnosis of gall-bladder disease to old and well-tried methods as the most useful; to careful and painstaking history and to such facts as we can elicit by the unaided senses—by sight and by touch particularly. We do not neglect any possible laboratory or instrumental aid, but we place most reliance on what the patient tells us and on what we see and feel for ourselves.

## INVOLVEMENT OF THE AURICLE AND CONDUCTION PATHWAYS OF THE HEART FOLLOWING INFLUENZA.<sup>1</sup>

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DURING the past year a number of interesting postinfluenzal cardiac conditions, late results of the 1918 influenza epidemic and more recent complications of the epidemic of 1920 have been observed and studied in the electrocardiographic laboratory of the Michael Reese Hospital. Certain of these cases throw light on the mode and site of action of the influenza poison on the cardiac mechanism, particularly on the auricle and conduction system, and clarify, to some extent, the more general statements of observers in the earlier epidemics. It is for this reason that the following cases are reported.

A number of suggestive studies have already appeared, Lucke, Wight and Kime<sup>2</sup> from a detailed study of necropsies from 126 definitely proved fatal cases of influenza, concluded that in the majority of instances acute parenchymatous changes of the myo-

<sup>1</sup> Read at the Meeting of the Association of American Physicians, Atlantic City, May 4, 1920.

<sup>2</sup> Pathologic Anatomy and Bacteriology of Influenza, Arch. Int. Med., 1919, xxiv, 154.

cardium, similar to the changes of other acute infectious diseases, occurred. In over 90 per cent. of these cases more or less relaxation of the right heart was present; in over 88 per cent. an associated cloudy swelling occurred. Microscopically they found acute parenchymatous degeneration and vacuolization. While these cases represented the fatal ones it may be inferred that in the less seriously ill patients the heart is similarly affected, though to a less degree.

Other reports, although not as conclusive as the above, admit some degree of myocardial involvement. For example, Hart,<sup>3</sup> although believing that the cyanosis and death in influenzal bronchopneumonia is not primarily cardiac in origin, admits that in the few uncomplicated cases in which the heart was carefully studied a moderate degree of myocardial degeneration was found. Smith,<sup>4</sup> in a study of postinfluenzal tachycardias at Camp Travis, concluded that organic heart disease was not the basis of the tachycardia and quotes various autopsy reports from army camps as to the infrequency of myocardial involvement, judged largely from gross appearances. Later, however, he states "It is possibly true that pathologic changes, sufficient to cause serious disturbances in later life, could have easily been overlooked with the naked eye."

A somewhat similar conflict between clinical and necropsy findings may be found in Sir James Mackenzie's discussion of "Cardiac Complications of Influenza,"<sup>5</sup> wherein he states that "if one looks at the heart postmortem in these fatal cases one sees the extensive damage done to the myocardium," and continues, "It is possible that influenza may lay the beginnings of a myocarditis which ultimately leads to heart failure, but I have not seen this occur in the many cases I have met in general practice." He concludes, in reference to the late effects: "The weakness after influenza is not, properly speaking, cardiac in origin, but is the outcome of an injury to other systems as well as the heart, such as the central nervous system. Even when we find such marked abnormalities as increased rate, systolic murmur, increase of size of heart and extrasystoles the cause of these signs ought not to be looked upon as heart disease, but merely as manifestations of general illness." In reference to the effect of influenza on patients with chronic heart disease, Mackenzie states, "I never found that influenza injured them in any way. Everyone, even those with advanced heart failure, passed through the attack scathless."

Thomas Lewis,<sup>6</sup> however, takes issue with Mackenzie in the follow-

<sup>3</sup> The Heart in Bronchopneumonia: Observations on the Activity of the Heart and its Response to Digitalis Made during the Recent Epidemic, *AM. JOUR. MED. SC.*, 1919, clviii, 649.

<sup>4</sup> Tachycardia Following Influenzal Pneumonia, *Jour. Am. Med. Assn.*, 1919, lxxiii, 1685.

<sup>5</sup> Cardiac Complications of Influenza, *Practitioner*, 1919, cii, 19.

<sup>6</sup> The Soldier's Heart and the Effort Syndrome, New York, 1919.

ing words: "The relation of infection to the cases of real heart disease must also be emphasized. It is of first importance. Nothing jeopardizes the condition of a heart patient more than infection, be the infection rheumatic fever or infection expressed as tonsillitis, influenza, bronchitis, etc. During the recent influenza epidemic the infection spread to a ward reserved for cases of serious heart disease. We lost two patients, and the lives of several others were seriously jeopardized."

These several studies are sufficient to emphasize the diversity of opinion regarding the effects of influenza on the heart, notwithstanding which some degree of uniformity of opinion is beginning to crystallize and may be expressed as follows:

1. Necropsies of fatal cases of influenza, in spite of slight gross pathologic changes in the heart, show rather universally acute parenchymatous degeneration and vacuolization, and, at times, extensive myocardial damage. Group I.

2. Clinical studies during the acute stage of illness, and in convalescence, indicate a rather remarkable recoverability of complete cardiac function. The postinfluenzal flabby heart muscle gradually disappears under graduated and properly directed exercise. Several of our cases are of this type. Group II.

3. Certain of these acute myocardial processes, however, do not clear up, at any rate for a very long time, and become cases of true postinfluenzal myocardial insufficiency. The present cases for the most part fall into this last group. Group III.

A very few electrocardiographic studies in influenza have appeared. Cockayne's<sup>7</sup> description of heart-block and bradycardia is of special interest in this connection. He found that simple bradycardias were caused by a poisoning of the myocardium, especially the sino-auricular node; the cases of heart-block result from the poisoning of the muscle of the auriculoventricular bundle; while two cases of marked bradycardia with prolonged *A-V* interval were due to the involvement of both sino-auricular and auriculoventricular areas. He reports one boy, aged sixteen years, with sinus block, who had a mild right-sided postinfluenzal pneumonia that cleared up entirely in twenty-eight days. The prolonged *A-V* ("P-R") cases appeared in mild pneumonias and lasted from nine to twenty-three days. Nine cases of two to one heart-block were observed, lasting from one to thirty-three days. Six cases of three to one heart-block averaged fourteen days. The onset of the bradycardia usually occurred after the temperature had become normal. Most of the patients were young men suffering from mild influenzal pneumonia. After six weeks only one complained of cardiac symptoms. None showed any undue irritability of the heart.

<sup>7</sup> Heart-block and Bradycardias Following Influenza, *Quarterly Jour. Med.*, 1919, xii, 409.



CASE I.—S. R., teamster, aged twenty-five years, married, entered the hospital August 20, 1919, complaining of moderate shortness of breath and precordial discomfort varying in intensity, necessitating, at times, rest in a recumbent posture. He was in robust health up to April, 1919, at which time he had a moderately severe attack of influenza, with temperature  $101^{\circ}$  to  $102^{\circ}$ . Against

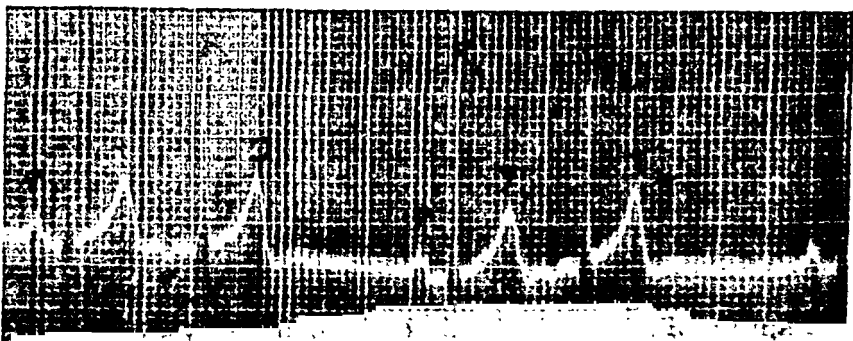
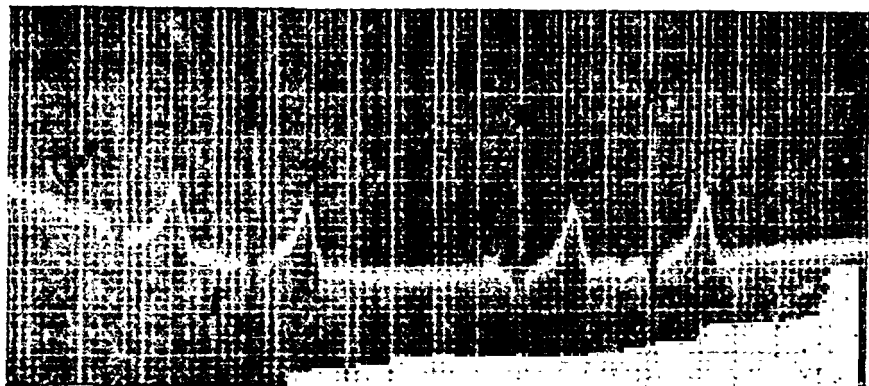


FIG. 1.—Case I. S. R. Postinfluenzal myocarditis. Pulsus bigeminus caused by regularly recurring auricular extrasystoles—ectopic—(inverted) auricular contractions ( $P_2$ ) following normal contraction of the auricle ( $P_1$ ).

the advice of his attending physician he remained home only three days, returning to his work as a teamster while not entirely free from fever. Two weeks later the above complaints occurred. He is a moderate smoker. Examination of his heart shows the apex in the fifth interspace, the left border 10 cm. the right 4 cm. from the mid-sternal line. Heart tones irregular, occurring in groups of two, pulsus bigeminus, no murmurs. His systolic blood-pressure was

115 mm. Hg, diastolic 55 mm. Hg. The urine was negative, blood negative and blood-Wassermann negative. Electrocardiographic examination showed a pulsus bigeminus due to regularly recurring auricular extrasystoles, "P" being inverted, "ectopic," every second auricular beat (Fig. 1). At the present (April, 1920), one year after his influenza infection, patient is able to take care of a small newsstand, to which occupation he was advised to change because of inability to work as a teamster. Recent examination

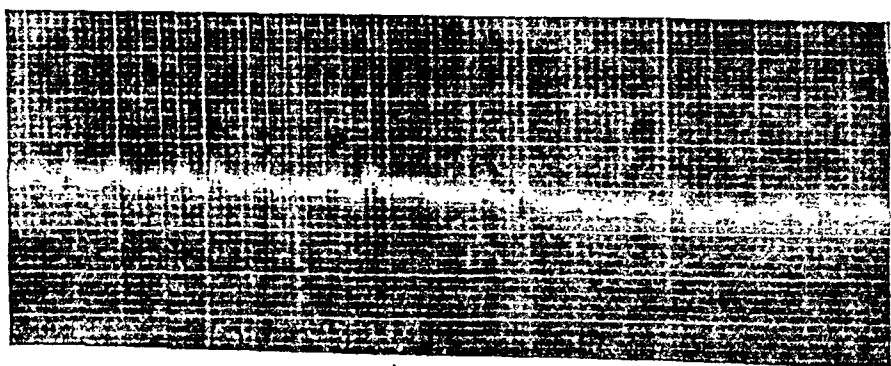
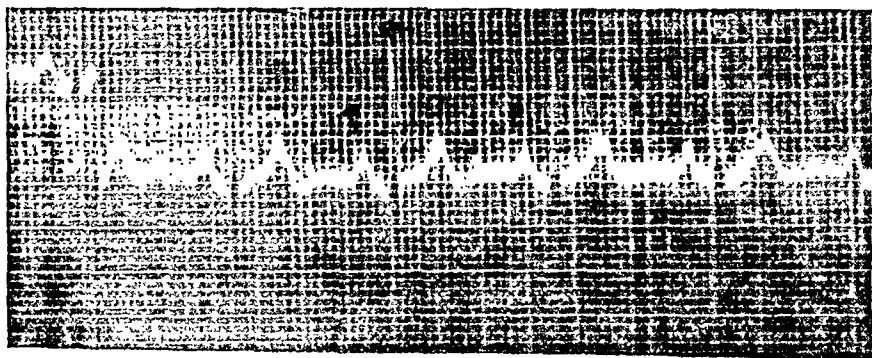


FIG. 2

at the dispensary showed a perfectly normal pulse when at rest, which, however, promptly changed to bigeminus following slight exertion, sitting up and lying down, on the examining table. Summary: Postinfluenzal auricular myocarditis, pulsus bigeminus, auricular extrasystoles. Group III. Duration twelve months.

CASE II.—Dr. S., Mobile, Alabama, aged thirty-eight years, physician. He entered the Medical Reserve Corps of the army in June, 1918. In October he had a moderately severe attack of

influenza, without pneumonia, but with complicating frontal sinusitis. Since the influenza he has noticed a slight dyspnea, particularly on playing golf. He believes his endurance low and notices

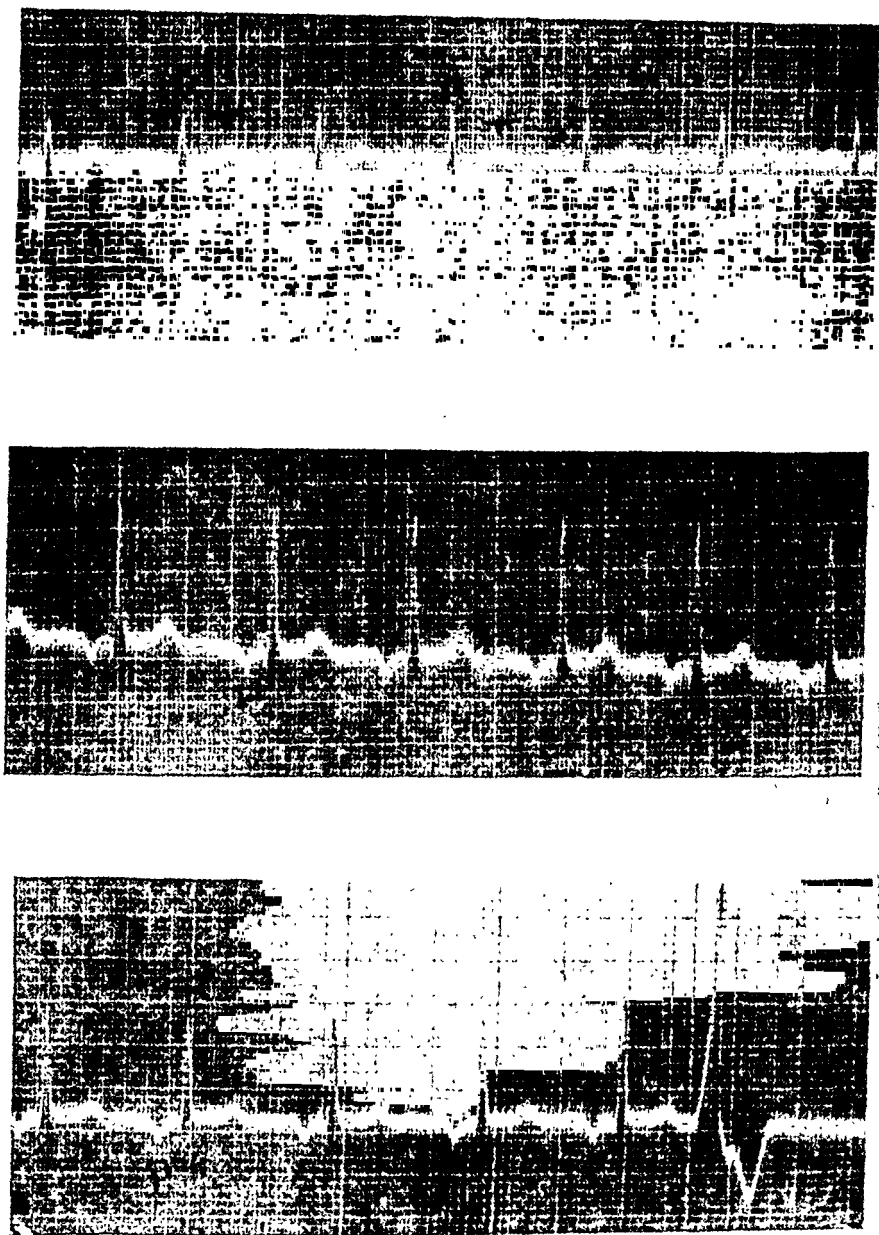


FIG. 3

that he tires easily. When previously he was able to work without fatigue from seven in the morning to twelve at night he now scarcely can get through his day from eight in the morning to three in the

afternoon. He still complains of frontal headache. There is no precordial pain or edema of the ankles. His systolic blood-pressure is 150 mm. Hg, diastolic 90 mm. Hg. His right heart measures 3 cm., his left  $11\frac{1}{2}$  cm. from the midsternal line. The pulse was 88, the heart tones regular and clear; there were no accentuations or murmurs. Immediately after exercise his pulse increased to 132, after two minutes to 128, after five minutes to 112 and after ten minutes to 100. His urine showed two plus albumin, microscopic negative; leukocytes 6800. The electrocardiographic examination showed "P" high in L. I, II. and "R" low and notched in L. III. (Fig. 2). Diagnosis: In view of the poor response to effort, marked fatigue, dyspnea, albuminuria and electrocardiographic findings a diagnosis of postinfluenzal myocardial insufficiency. Group III. Duration fourteen months.

CASE III.—C. H. W., aged thirty years, merchant, had a mild attack of influenza in September, 1918, and a recurrence in November, 1918. In neither attack, although there was a rise of temperature, did he take to his bed. Following the last attack he noticed a marked loss of endurance and an irregularity of his pulse. Examination of his heart was entirely negative except for an occasional extrasystole before exercise at long intervals. Exercise tests (hopping fifty times on one foot) showed a pulse of 93, systolic blood-pressure 122 mm. Hg, diastolic 75. Immediately after exercise the pulse was 126, systolic pressure 135, diastolic 65. Two minutes after exercise the pulse was 95, systolic pressure 118, diastolic 65. Electrocardiographic examination (Fig. 3) shows absence of "P" in L. I. and inversion of "P" in leads 2 and 3, extrasystole of right ventricular origin in L. III. Diagnosis: In view of fatigue not felt before the attacks of influenza, extrasystoles and electrocardiographic findings a diagnosis of postinfluenzal auricular and ventricular involvement was made. Summary: Postinfluenzal, right ventricular extrasystoles and "ectopic" auricular contractions. Group III. Duration fifteen months.

CASE IV.—Dr. B., aged twenty-eight years, house physician, entered the hospital March 3, 1920, complaining of sore-throat, with a history of attendance on several nurses who had been on duty in the influenza wards and who had become ill, suffering with sore-throat, temperature and generalized pain. Dr. B. complained of pain in his knee-joints, palpitation, sensation of "heart stopping," moderate frontal headache and nasal discharge containing pure *Streptococcus hemolyticus*. The past history revealed the usual exanthemata of childhood and a moderately severe attack of rheumatism of three weeks' duration following sore-throat seventeen years ago. The mother died of a cardiac lesion at the age of thirty-

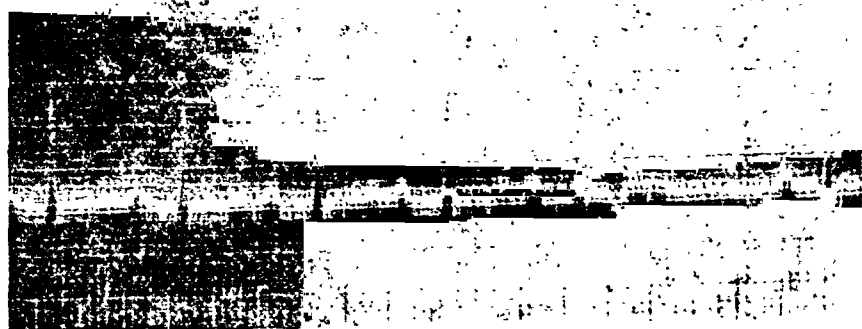
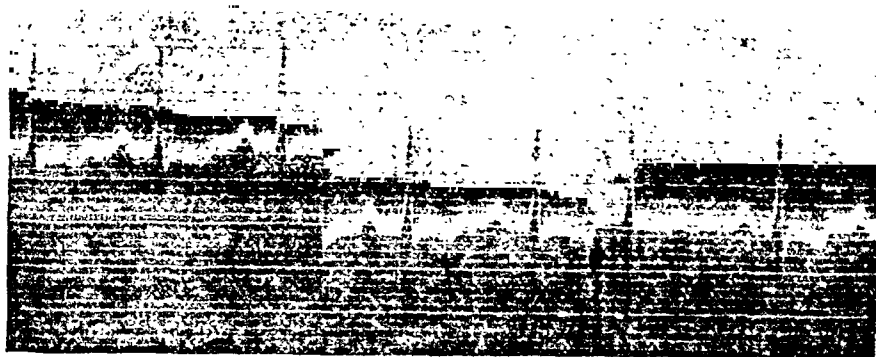


FIG. 4

three. The father had attacks of rheumatism. Examination showed a large, well-nourished, obese young man, lying quietly in bed without evidence of respiratory or cardiac embarrassment, with purulent nasal discharge. Examination of the heart showed no evidence of gross circulatory failure. The pulse-rate was seventy, with an intermittence about every thirty beats. The quality was soft and compressible, the apex fifth interspace, feeble, no thrill. The left border was inside the nipple line, the right border at the right sternal margin. The heart tones were soft and there was no murmur. There was no edema of ankles. March 4 the pulse was irregular and there was some swelling of the knee-joints and small joints of the feet. The electrocardiographic report (Fig. 4) showed moderate left preponderance, diphasic "P" in lead I, and auricular extrasystoles. P-R .20, rate 109.

Electrocardiogram March 16 (Fig. 4) shows auricular extrasystoles, dropped beats, P-R .32 to .36. Rate 96. Progressive lengthening of P-R.

Electrocardiogram March 22 (Fig. 4) shows the blocking of an auricular extrasystole. P-R .24, rate 88.

Electrocardiogram March 26 (Fig. 4) shows P-R, averaging .24, pulse 90, auricular extrasystoles arising in the neighborhood of sinoauricle node. P. T. Superimposed. Electrocardiogram, April 20, shows normal cardiac mechanism.

Summary and Diagnosis: Acute streptococcus myocarditis involving particularly the auricle and conduction pathways producing chronologically, ectopic auricular extrasystoles; involvement of the auriculoventricular bundle with delay in the P-R interval and occasional dropped beats (early heart-block); blocking within the auricle of ectopic extrasystoles; auricular extrasystoles arising in the immediate neighborhood of the sinoauricular node. Group II. Duration six weeks.

CASE V.—Miss E. S., pupil nurse, aged twenty-three years, entered the hospital March, 1920, complaining of sore-throat and loss of weight. Since a septic sore-throat December 19, 1919, containing hemolytic streptococcus, she had had more or less throat infection and felt weak on slight exertion and tired easily. Examination showed the hands and face to be very pale, anxious facies, apparently suffering, hands held over the heart, respirations shallow and superficial, pulse 114. She complained of gripping pain over the heart that made speech and breathing difficult. She said that she could feel her pulse become slow and irregular, after which attacks the pulse became more rapid. There was a marked tenderness in the fifth interspace. The apex lay within the nipple line in the third and fourth interspace. The heart tones were irregular. There were no murmurs. An electrocardiogram taken

March 3 (Fig. 5) showed a three to two heart-block, rate 62 of the ventricle. An electrocardiogram taken the following day showed nodal rhythm, rate 89.5 (Fig. 5).<sup>8</sup> March 9 the heart seemed normal,

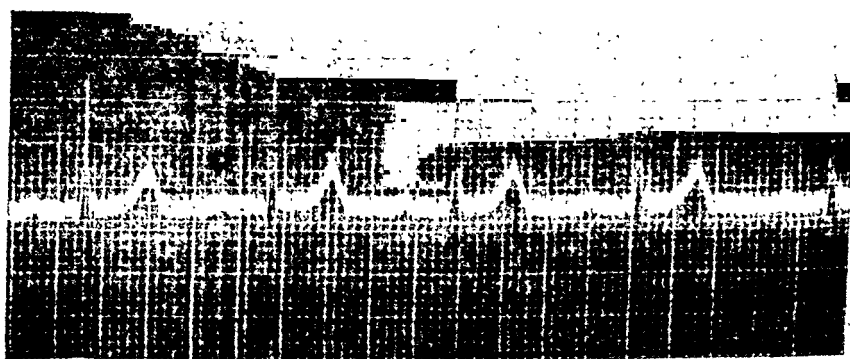
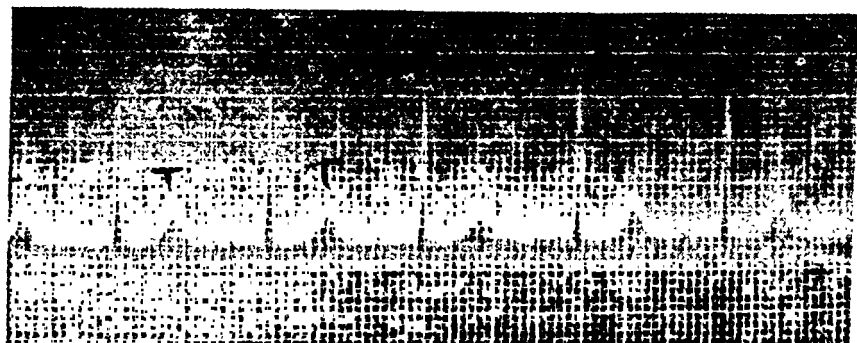


FIG. 5

<sup>8</sup> Dr. Robinson, who kindly looked over this curve, believes it more likely markedly delayed P-R interval with P buried in the T complex.

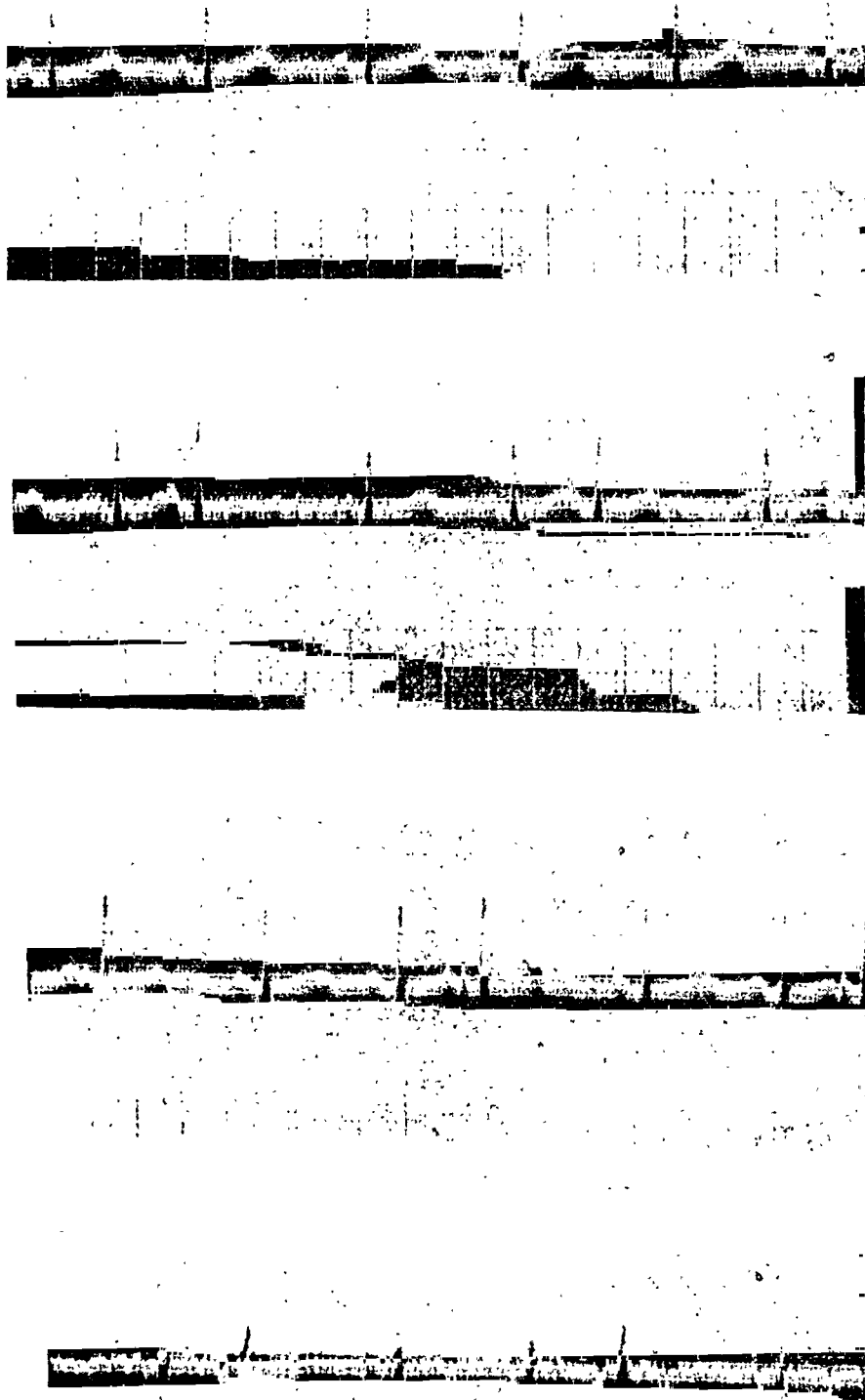


FIG. 6



there were no accentuations and the first sound was barely perceptible. The electrocardiographic examination showed P-R .25, rate 65.2. One week later examination showed normal cardiac mechanism. Summary and diagnosis: Acute streptococcus myocarditis involving primarily the bundle with three to two partial heart block, later nodal rhythm, with anginal attacks. Group II. Duration two weeks.

**CASE VI.**—Miss H. N., stenographer, aged twenty-eight years, has had "heart trouble" since the "flu" in October, 1918. Remained in bed three weeks during attack; there were no lung complications, but some cardiac irregularity during acute illness. Remained home two months convalescing. In the spring of 1919 complained of same precordial uneasiness with slight pain, relieved partially by digitalis.

January, 1920, again complained of pain in heart region; no dyspnea or pain with effort; some palpitation. At times has some throbbing sensation in left arm. Has lost six pounds past few weeks, tires easily, gets extremely fatigued.

*Past Illnesses.* Scarlet fever eight years ago. Inflammatory rheumatism at twelve years of age in knees and elbows; recurring tonsillitis; tonsillectomy five years ago.

*Examination.* Right heart  $3\frac{1}{2}$  cm. left 12 cm. midsternal line. Arrhythmia (extrasystoles) left border just outside nipple line.

*Electrocardiograph.* Auricular extrasystoles in all leads arising in neighborhood of pacemaker, number possibly increased after atropine.

*Summary.* Chronic postinfluenzal myocarditis, with localization in the auricle, resulting in auricular extrasystoles. Duration seventeen months. Group III.

**Discussion.** The above cases, cited as examples from a larger group, are offered as evidence that the acute epidemic respiratory infections known as influenza, cause damage to the cardiac mechanism, which may be demonstrated clinically and electrocardiographically. As observed by the latter method these infections affect, for the most part, the auricle and conduction pathways of the heart, although clinically it may be supposed that ventricular involvement also occurred. Unfortunately no gross or microscopic pathologic material was available for study. Cases IV and V, in which hemolytic streptococci seemed to be the predominant etiologic organisms, are strikingly similar to Cockayne's cases of influenzal poisoning of the sino-auricular node and auriculoventricular bundle, thereby substantiating the influenzal involvement of the auricle and the His bundle.

One feels justified in concluding that at least in a certain percentage of cases, acute influenza (streptococcus) picks out early and to a degree exclusively the auricle and conduction pathways.

Barker's<sup>9</sup> recent interesting case of arrhythmia with auricular involvement following focal infection may still further broaden our views as to the general point of attack of infectious agents and poisons on the cardiac mechanism.

**Conclusions.** 1. Six cases of postinfluenzal myocardial involvement are reported, involving particularly the auricle and conduction pathways of the heart.

2. From a survey of the literature together with clinical and electrocardiographic studies, a grouping of postinfluenzal cardiac complications is offered as follows:

(a) Fatal cases showing acute parenchymatous degeneration and vacuolization of the myocardium.

(b) Non-fatal, acute cases, showing involvement of auricle and conduction system during height of infection, with complete restoration to normal cardiac mechanism with subsidence of infection. Duration two to six weeks.

(c) Non-fatal chronic cases with arrhythmia and involvement of the auricle persisting and causing partial invalidism long after subsidence of acute infection. Duration twelve to seventeen months—plus.

3. Suggestion is offered that acute respiratory infections (Influenza, Streptococcus) single out early the auricle and conduction pathways of the heart.<sup>10</sup>

Appreciation to several members of the Hospital Staff is herewith offered, for permission to publish curves of their cases, and in particular to Miss Marguerite Collver, laboratory technician, for invaluable aid in the preparation of this material.

## DETERMINATION OF THE NEED OF SURGERY IN PEPTIC ULCER, WITH REMARKS ON GASTRO-ENTEROSTOMY.<sup>1</sup>

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A STUDY of surgical statistics would convey the impression that in operative procedure we have a dependable cure for gastric and duodenal ulcer; and last year before this Association, Alvarez said: "My own conviction after many years of seeing these ulcer patients

<sup>9</sup> Cardiac Arrhythmias, Arch. Int. Med., 1919, xxiii, 158.

<sup>10</sup> Probably the infections affect the whole heart similarly (cf. microscopic studies of auricle and ventricle), but due to other factors, such as thinness of the auricular wall, presence of ganglion cells or other unknown conditions, disturbances of auricle and conduction pathways first become evident.

<sup>1</sup> Read before the American Gastro-enterological Association, May 4, 1920.

returning with relapses is that our medical treatments do little if any good except in rare cases." Yet in our own practice ulcer cases that have had one or more operations come for treatment almost as frequently as ulcer cases that have not been operated upon; and other gastro-enterologists tell us that this is also their experience. Such antagonistic ideas, therefore, furnish our excuse for this presentation on a somewhat hackneyed subject.

Ulcer cases may require emergency treatment or they may not, and this fact divides them into two groups.

**I. The Emergency Cases.** The two striking emergencies which occur in gastric and duodenal ulcer are acute perforation and profuse hemorrhage. In acute perforation all will agree the earliest possible surgery is imperative.

In serious hemorrhage, on the other hand, it is generally the opinion that operative intervention is dangerous and mostly futile. Sir Berkeley Moynihan, in issuing a warning against hasty surgery, estimated that not more than 3 per cent. of profusely bleeding gastric and duodenal ulcers could be treated successfully by laparotomy. Lindberg, of Copenhagen, tabulated 68 cases of hematemesis so severe as to raise the question of an emergency operation. In all of the 68 surgery was decided against. Five died, and at autopsy it was found that not one of these could have been helped by surgery. On comparing these statistics with others from clinics where operation had been the choice, Lindberg was convinced that surgical measures are never indicated in cases of acute hemorrhage from the stomach or duodenum. We find that many surgeons have had the trying experience of opening a stomach in such a case and being unable to find the site of the bleeding. Lund, of Boston, said: "I have learned that it is poor practice, when the patient is depleted by hemorrhage, to open the stomach and try to grasp the artery in the bottom of an ulcer." Other surgeons speak in like manner.

Yet now and then one hears of a case in which life has undoubtedly been saved by surgery, as where perforation accompanied the hemorrhage or where the bleeding-point was readily found. We have in mind a recent case where a vein was held open by the indurated tissues and where undoubtedly death would have ensued had operation not been performed. And it is a trying experience, and one that seems inconsistent, for a physician to stand helplessly by while a patient vomits copious amounts of blood every hour or two and rapidly becomes exsanguinated under his very eyes. The difficulty lies in the fact that as these hemorrhages mostly cease spontaneously and are not fatal we prefer to wait, and then when we decide that the bleeding probably will not stop it is too late for surgery.

In any case, therefore, while applying the proper medical measures we should, when possible, prepare for transfusion. If the bleeding persists transfusion is the measure of choice. If transfusion fails

to stop the bleeding it at least puts the patient in better condition for surgery, which then, in our opinion, might be resorted to. Thus very few of the cases would come to surgery, but these few, being hopeless otherwise, might include a sufficient proportion of operable cases to justify the procedure. That is to say, the great risk of operative intervention and the small chance of helping by operation are overshadowed by the almost certain supervention of the patient's death if operation is not performed. In such a case the surgeon who fails is without blame.

**II. Cases not in the Emergency Class.** In the treatment of an ordinary ulcer case surgeons are not now so ready to operate as formerly, and many grant that judgment is required as to the need of surgery; for operation always produces a damaged abdomen and a damaged stomach with a new anatomy and a new physiology; it is followed only too often by undesirable sequelæ; and frequently enough it leaves the patient relieved for a time, only to have him return later with a recurrence of symptoms which, because of the surgical damage, may be more difficult to treat than before. As Connell expresses it: "The immediate result is invariably most encouraging, but relapse is far from uncommon."

We cannot here discuss the merits of the various surgical procedures, nor compare one with another, but because it is the usual operation we shall dwell briefly on the subject of gastro-enterostomy, referring you for much interesting data to the papers of Dr. Frank Smithies and Drs. Wilensky and Crohn, which have been read recently before this Association.

*Gastro-enterostomy.* "This operation," in the words of Frank Martin, "has been for years the cure-all for almost every stomach malady that exists." Of 261 ulcer cases returning for treatment after operation, Smithies found that gastro-enterostomy had been done in all. But among the best surgeons today it would seem to be considered of value only for ulcers of the duodenum and of the pyloric and antral regions, and not, except in rare cases, for ulcers in the body of the stomach or high up on the lesser curvature. Indeed, many eminent surgeons agree with Deaver that "when the ulcer is located elsewhere than at the pyloric end posterior gastro-enterostomy does little if any good." However, Mills has directed attention to the fact that in certain hypotonic types of stomach, after a V-shaped or sleeve resection for ulcer of the lesser curvature, a gastro-enterostomy is required; we also have seen the necessity for gastro-enterostomy in just such cases and Peck has expressed the opinion that it is a wise procedure. Sir Berkeley Moynihan has said "under no circumstances is the operation to be done in the absence of demonstrable organic disease." Yet this cannot be an absolute rule for we have had good results in a few rebellious cases of marked gastric atony without ulcer.

Among the various reasons advanced in surgical writings to justify

simple gastro-enterostomy those usually met with are the following: (1) That it relieves the pyloric end from muscular activity and from the irritation of food and gastric juice; (2) that it relieves the pyloric end from high peristaltic pressures; (3) that by being placed at the most dependent portion of the stomach it favors gravity drainage; (4) that it favors stomach emptying regardless of gravity drainage; (5) that by permitting the alkaline duodenal contents to flow back into the stomach it decreases gastric acidity. Let us consider these seriatim:

1. *That it Relieves the Pyloric End from Muscular Activity and from Food and Gastric Juice.* To emphasize the stress laid upon this factor, I would quote Richard Lewisohn, who wrote as late as 1918: "Even at the present day many surgeons consider gastro-enterostomy a safe procedure to keep food material away from the ulcer-bearing area." In the majority of cases the ulcer-bearing area is the antral, pyloric or duodenal region. Without giving the data in detail I might say that it has been shown repeatedly, both by laboratory experiments and by the roentgen rays (see 4 below), that after a gastro-enterostomy peristaltic waves occur in the pyloric end of the stomach the same as before the operation; that to a certain extent and sometimes in their entirety the food and gastric juice are swept past the new opening and take their normal course to the pylorus; and that vigorous churning takes place in this end of the stomach. In 262 postoperative cases Smithies found chymification after a mixed meal good or fair in 90 per cent. Therefore we may say that gastro-enterostomy does not result in relief of the pyloric end from muscular activity or from the irritation of food and gastric juice, though it probably lessens the degree of these.

2. *That it Relieves the Pyloric End from High Pressures.* It is at the antral and pyloric regions that normally intragastric pressure rises to the highest point. Moritz found the intragastric pressure at the cardiac end 6 to 8 cm. of water, and at the pyloric end 20 to 30 cm., with rhythmic rises to as high as 60 cm. Sick found the cardiac pressures 6 to 16 cm. and the pyloric pressures 25 to 42 cm., and von Pfungen, in a boy with a fistula in the midstomach, found the maximum pressure at the fistula 19 cm. and that at the pylorus 162 cm. In ulcer cases with hypermotility the pyloric pressure is probably quite high and in cases with hypermotility and pyloric obstruction, whether organic or spasmodic, the pyloric and antral pressures probably rise very high indeed. In pyloric obstruction without atony Crohn and Wilensky have shown that the hunger contractions may take on a spasmodic character, with correspondingly high intragastric pressures, a condition abolished by operation. They found that except in these obstruction cases hunger contractions were usually absent. Therefore, although it is agreed that in pyloric obstruction cases without atony gastro-enterostomy

results in lessened pressures on the ulcer area, yet in cases without obstruction this is by no means apparent. Certainly in Sick's case a midgastric fistula failed to relieve the pylorus from high pressure.

3. *That by being Placed at the Most Dependent Portion of the Stomach it Favors Gravity Drainage.* At operation we have repeatedly seen surgeons, imbued with this idea, strive to select the lowest point of the stomach; and, as Martin remarks, they even place the patient in upright posture after operation to favor drainage. The fact is that the lower border of the stomach changes considerably during digestion, in the nearly empty stomach the pylorus becoming ordinarily the lowest or almost the lowest part. Moreover, as the stomach fills it rotates on an axis extending from the cardia to the pylorus. It can hardly be supposed then that what is the most dependent point at operation in a stomach rendered atonic by the anesthetic and in a patient lying on his back, will remain the most dependent point for any length of time during the digestive period after the stomach has regained its tone and the patient is upright.

As a matter of fact, however, in the ordinary alimentary tract food is not propelled by gravity but by differential pressures. Cannon and Blake showed in cats that after gastro-enterostomy, even though the animal was held up so that the opening was in the most dependent portion, water placed in the stomach did not run by gravity through the stoma into the jejunum but passed through only in response to the force of peristaltic waves. Therefore, in the ordinary case, gastro-enterostomy does not favor drainage by gravity. In the emptying of highly atonic stomachs in atonic abdomens with low intra-abdominal pressure, gravity may play a distinct role; yet in these cases unless there is pyloric stenosis the results of gastro-enterostomy are not highly encouraging.

4. *That it Favors Stomach Emptying Regardless of Gravity*, that is, by peristalsis. In regard to this I find a great discrepancy of opinion. In the roentgen-ray studies of Cannon and Blake on cats fed with fluid boiled starch the food passed regularly through the pylorus and not through the new stoma, with two exceptions, one where the stoma was in the vestibule close to the pylorus and the other where the stoma was large and in the anterior wall about half-way between the two ends of the stomach. Except for these two cases the pylorus was regularly the exit chosen, even though it was much narrowed by a ligature. This was in animals with no ulcer to cause hyperperistalsis and abnormality of pyloric closure. That both in man and laboratory animals the food mostly does pass the new opening to seek the natural outlet has been shown by others, *e. g.*, Tuffier, Delbet, Kelling, Guibe, Troell and Lewisohn; and Haertel, after the study of a large series of radiographs following gastro-enterostomy in man, observes that though in most cases food passes through both the pylorus and the new stoma, yet the peristaltic

wave is unchanged and continues to be directed as before toward the pylorus. Schueller, Petrén, Cole, Carroll and other radiographers have made similar observations.

On the other hand recent reports by C. H. Mayo, Carroll, Hartmann and Outland, Skinner and Clendenning point to the effectiveness of the gastro-enterostomy stoma; and Carman and Balfour, of the Mayo Clinic, emphatically state that the opaque meal regularly passes freely through the stoma even after years. Several observers have remarked, however, that while in the first few weeks after operation the food has taken its exit for the most part through the new outlet, yet later it has returned in large measure to the outlet through the pylorus. This might be explained by assuming that in the first few weeks the ulcer is still in the irritative stage and is effective in producing pyloric obstruction by pylorospasm; but that later, as the ulcer heals, it no longer excites pylorospasm, and therefore, as there is no longer obstruction, the food passes through the natural outlet. This would seem to be the desirable sequence of events. Truesdale showed that in some cases after the operation the pylorus, owing to disuse, undergoes atrophy and dilatation and remains permanently open. It is interesting to note how frequently in some of the relieved cases the roentgen-ray shows a six-hour residue. Smithies found an eight-hour food residue after a mixed meal in 16.4 per cent. of those returning for treatment. Carter notes an early emptying time when both pylorus and stoma are patent but delayed emptying when the pylorus is occluded at the operation. Wilensky and Crohn state that the emptying power of the stomach is not accelerated by gastro-enterostomy with pyloric blocking, but is actually retarded.

5. *That Whatever Good is Obtained is Due to the Diminution of Acidity* by the passage of bile and pancreatic juice into the stomach through the new stoma. It is Deaver's opinion that if a posterior gastro-enterostomy in ulcer of the pyloric region does any good at all it is by allowing bile and pancreatic juice to enter the stomach, thus producing a neutralizing effect on the acid contents. This is the opinion of many surgeons. It is true that following gastro-enterostomy the acidity tends to be reduced, for H. J. Paterson found that it falls on the average thirty points, and Smithies, in those returning for treatment after operation found a reduction in free acid and total acidity in about 80 per cent., the reduction averaging about twenty points, though in 17 per cent. there was no reduction and in 3 per cent. a rise in acidity. One month after operation Crohn and Wilensky found a slight average decrease in acidity though not a decrease in all cases.

**The Effect of Bile and Pancreatic Juice on Acidity.** Grey demonstrated by cholecystogastrostomy that when the total output of bile was made to pass through the stomach it did not materially affect the level of gastric acidity. He also deflected the total pan-

creatic juice into the stomach and likewise noted no material change in acidity. In a study of fractional curves after gastro-enterostomy Wilensky and Crohn observed that the influx of bile was frequently followed by a secondary rise in acidity and that at times the highest acidities were recorded when the bile was present in greatest abundance. These observations tally with our own experience and that of Smithies, that highly bilious stomach contents after gastro-enterostomy frequently show high acidities. H. S. Carter and Wilensky and Crohn have reported that a number of the operated cases gradually lowered their acidity until a complete achylia was developed. This could hardly have been due to a reflux of alkaline material. Therefore though acidities tend to be lower after gastro-enterostomy, they are not by any means always lower, and we do not believe that the diminished acidity is the effect of neutralization by regurgitated bile and pancreatic juice. As a matter of fact the degree of gastric acidity is unimportant in deciding the improvement after operation (Troell, Crohn).

To summarize our remarks on the desired effects of gastro-enterostomy we might say that *when there is obstruction* to the exit of food the operation permits stomach emptying and relieves the retention. But in *non-obstruction cases* it does not, at least to any great extent, relieve the ulcer-bearing region from peristaltic activity from the irritation of food and gastric juice and from high peristaltic pressures, it does not favor gravity drainage, it does not, as a rule, accelerate the emptying time, and it does not act through the neutralization of high acidity by the bile and pancreatic juice which it permits to enter the stomach. Therefore, except in cases of obstruction, due either to disease or to operative procedure, as in pyloric stenosis or pyloric removal and possibly hour-glass contraction, we are unable to discover a satisfactory reason for a good result from gastro-enterostomy. It would therefore seem a pertinent question to ask: Except in the presence of obstruction what useful function does gastro-enterostomy perform?

**Gastro-enterostomy with Pyloric Blocking.** On account of the numerous failures of gastro-enterostomy, and the frequency with which after gastro-enterostomy the food has passed in the normal direction through the pyloric exit even when this was partially obstructed, a number of surgeons have attempted to block the pylorus by means of a silk ligature. W. J. Mayo has concluded that such blocking gives no advantage, and this belief is concurred in by Scudder, Gonnerud and others; and as it has not been a successful procedure, it has largely been abandoned. But in its place has come pylorotomy or at least a severance of the duodenum from the pylorus. To this certain surgeons object, on the ground that it makes the operation a more severe one; that it makes a permanent obstruction no longer needed when the ulcer heals; that it favors high pressures in the ulcer-bearing region, and possibly that by



preventing the contact of hydrochloric acid with the duodenal mucous membrane, it prevents the formation of secretin, and hence results in a diminished secretion of pancreatic juice and bile. We do not think this last a factor, for three reasons, namely: (1) The absence of hydrochloric acid in cases of gastric achylia is not accompanied by a decrease in the secretion of bile and pancreatic juice; (2) hydrochloric acid can produce secretin in the jejunal mucous membrane, as shown by Bayliss and Starling; (3) in these cases there is obviously no lack of bile and pancreatic juice.

In several of our own cases, after a simple gastro-enterostomy had failed to relieve, a secondary operation was done to block the pylorus. We can recall two in which the ulcer had been well up on the lesser curvature and had been excised by the saddle incision, but pylorospasm persisted. They did well after the pyloric excision. We can recall three others in which the ulcer was at or near the pylorus, and the pylorus at operation seemed well stenosed, but the symptoms continued after the gastro-enterostomy. All did well after pyloric obliteration.

**Normal Results of Gastro-enterostomy.** A gastro-enterostomy regularly results in certain changes, namely: (1) The passage of the acid and sometimes highly acid gastric contents into a jejunum which is habituated only to material that is alkaline; (2) admixture of the gastric contents with the bile and pancreatic juice at an abnormally low point in the intestine; (3) the passage of some poorly disintegrated food into a jejunum accustomed to receiving material that is well chymified. After a mixed meal Smithies found with the stomach tube that the gastric contents showed poor chymification in only 10 per cent. of the cases; yet it would seem that, owing to the position of the stoma, some of the food must be forced through without chymification.

**Untoward Sequelæ of Gastro-enterostomy.** The most common untoward sequelæ are: Renewed ulcer symptoms, retention symptoms, nausea and fulness without retention, pain, and diarrhea.

**Renewed Ulcer Symptoms after Gastro-enterostomy** may result from: (1) Failure of the original ulcer to heal. After a remission of a few weeks or months brought about by the rest and diet following operation and similar to remissions after medical treatment the symptoms recur.

2. The development of a new gastric or duodenal ulcer.

3. The development of a true peptic ulcer in the jejunum below the stoma region.

4. The development of ulceration in or about the gastro-intestinal anastomosis. This is probably due in most instances either to trauma from the use of clamps as demonstrated by Troell, Coffey, White and Hamilton or to the employment of unabsorbable sutures. Pool, W. J. Mayo, Mann, Gonnerud, Woolsey and others have reported finding the linen or silk sutures projecting from the bases

of such ulcers. It may be due to careless feeding in the early post-operative period, for in a study of gastro-enterostomy in animals, Flint found the new-formed anastomosis to be the site of a healing ulcerated surface for about two weeks.

*Retention symptoms* may result from failure of the stoma or obstruction of the jejunum, because:

1. The opening is too far to the left.
2. The opening shrinks unduly. Finney had a case in which in spite of absolute pyloric stenosis the stoma had been reduced to the size of a straw. Von Eiselberg believes that reduction in size of the opening is almost always due to ulceration.
3. The opening is closed by distention of the stomach, which causes stretching of the jejunum over the stoma. Cannon and Blake noted in cats that when the stomach was distended by a large meal the food passed through the stoma with difficulty, so they excised a gastro-enterostomy stomach, tied its pylorus and filled it with water. As the gastric wall became stretched almost no water escaped through the stoma, the comparatively small jejunal wall having flattened out over the opening to become practically a part of the stomach wall.
4. The opening is closed by contraction against it of the cut circular fibers of the jejunum. In the words of Cannon and Blake: "The contraction of the cut circular muscles can have no other effect than to shorten and flatten the intestinal wall between the two lines of attachment." In two of our cases opened under local anesthesia vigorous peristaltic waves were present, and after the anastomosis had been made we observed that as each wave reached the cut in the jejunum the whole wall of the gut flattened against the opening, the effect of the contraction of the circular fibers that had been cut being just that described by Cannon and Blake. It was obvious that anything in the duodenum would shoot up into the stomach rather than pass into the distal limb of the jejunum.
5. The stoma or the jejunum is closed by volvulus or traction, as when the stomach recovers from its operation atony or when the patient reassumes the upright position.
6. The food fails to pass readily into the distal limb of the jejunum because of adhesions with kinking. The circular muscles proximal to this point being cut and stomach peristalsis being absent for many days following operation (Wilensky and Crohn), there is no driving peristaltic force to push the food along, break newly forming adhesions and straighten out a kink (Cannon). We have had two marked cases of obstruction by adhesions with pocketing of the jejunum at a distance of two or three inches beyond the stoma, the roentgen-ray showing immediate passage of food from the stomach, but partial obstruction at the lower point with pouching above.
7. The establishment of a vicious circle, the food that passes through the still open pylorus travelling back into the stomach

through the stoma. Cannon and Blake watched such a process for half an hour, during which time not an atom of food passed into the distal limb of the jejunum. They noted no untoward results from the vicious circle. Vicious circle is usually due to a plastering of the jejunal wall against the opening or to obstruction of the distal limb of the jejunum. Probably it is a cause of untoward symptoms less frequently than usually supposed.

**Nausea and Fulness without Retention** may result from: (1) Too rapid emptying of the stomach. In feeding with the duodenal tube it has been found that passage of the food too rapidly or at a temperature much above or below that of the body is prone to result in feelings of distention, nausea, weakness or even collapse, symptoms quite the same as in occasional cases after gastro-enterostomy. (2) Possibly though not certainly from too abundant regurgitation of bile. In practically all cases after gastro-enterostomy bile is regurgitated into the stomach yet no nausea ensues. But in two striking cases during the periods of nausea we have noted excessive quantities of bile in the stomach contents, while in the same patients when free from nausea there was very little bile. We have been inclined to attribute the nausea to the abundant bile in the stomach though it is possible that the responsible factor may have been something else, the extra bile having regurgitated as the result of gagging. For though bile when swallowed is nauseating, yet fresh ox-bile has been administered by stomach tube by John Gerster without nausea.

*Pain* is usually the result of ulcer or adhesions, especially adhesions to the anterior abdominal wall.

*Diarrhea* is probably a sequel either to a too rapid emptying of the stomach, to irritation of the jejunum by either the acid stomach contents or coarse food particles, to changes in the pancreatic secretion, or to a superabundance of fat in the food (Cameron).

From Matthieu's Clinic at the St. Antoine, Paris, it was reported that very few if any of their cases of gastro-enterostomy, if followed over a sufficiently long time, failed to show some pathologic symptoms, gastric or intestinal.

In a study of cases following posterior gastrojejunostomy with exclusion or removal of the pylorus, Wilensky and Crohn found that 11 did well after the operation, though it was necessary to curtail the amount of food permitted, 14 showed definite disturbances in physiology and 7 showed mechanical disturbances in the functions of the gastrojejunal stoma. In almost all there was absence of peristalsis one month after operation.

In the group that apparently did well motility and acidity were slightly diminished and there was a distinct and persistent hypersecretion.

In the group with physiologic disturbances there were mental depression with poor nutrition, pain, vomiting, occasionally hema-

temesis, and constipation or rarely diarrhea. There were definite delay in motility, hypersecretion with a high acidity curve to the end of digestion and a poorly functioning stoma, produced not by stomal closure but by disturbed muscular function.

In the group with mechanical or organic changes at the stoma there were markedly delayed motility with retention, a high acidity curve, violent peristalsis, six-hour roentgen ray residue and insufficient or closed stoma.

**Summary.** Considering all the possibilities we have mentioned and other postoperative complications, such as hernia, rectus diastasis, gastro-intestinal fistula and various unmentioned abdominal adhesions, and in addition the operative mortality and the number of cases that after a period of relief show relapse similar to that following medical relief, we must feel that surgery in an ulcer case must not be too lightly resorted to. As Wilensky and Crohn say, "It is evident that the impression that gastrojejunostomy is an operation which in no way impairs the functional efficiency of the stomach is an erroneous one. In only a minority of the cases does the stomach return to an almost normal state of functional activity."

We do not wish, however, to disparage the use of the operation in the proper case, and would say with Crohn that we could not treat disorders of the stomach without using gastro-enterostomy. But its value is to make an exit for food when the normal exit is not available. And we hold with Torek that "the treatment of ulcer of the stomach is essentially medical and not surgical, and that it is only certain of its complications or sequelæ that require surgical intervention." We now leave the subject of gastro-enterostomy.

*Cases of Ulcer which Require Operation.* The emergency cases we have already considered. Of the others we have those in which surgery is imperative from the outset and those in which surgery should be resorted to only after thorough medical treatment.

*Surgery Imperative.* We consider surgery imperative and medical treatment futile in the following conditions, namely: (1) Chronic penetration as shown by radiographs; (2) palpable induration; (3) adhesions which cause distortion of the stomach, interference with peristalsis or much pain during the digestive period; (4) permanent hour-glass; (5) pyloric stenosis not syphilitic; (6) repeated copious hemorrhages; (7) conditions which suggest that an ulcer is becoming carcinomatous. In duodenal ulcer, as carcinomatous change rarely occurs, this is not of moment; but since in gastric ulcer this change is not infrequent, its possibility must induce an earlier consideration of surgery.

*Surgery only after Expert Medical Treatment.* The majority of peptic ulcer cases can, in our opinion, be definitely said to require surgery only after the failure of thorough and prolonged medical treatment. When a case is medical the relief of symptoms (not the

cure) by treatment is, as a rule, quite prompt. Therefore, on the one hand, the failure of the treatment to relieve the symptoms suggests that the case is probably surgical; whereas, on the other hand, when a case seems in all likelihood surgical, but not certainly so, a course of medical treatment is advisable to prove the point. Furthermore, if the patient shows a positive Wassermann reaction or gives a history or any physical evidence of syphilis, antileptic treatment should be tried.

Given a thorough medical trial by someone competent to supervise the treatment, we should consider those cases surgical which continue to show: (1) Persistent or recurrent hemorrhage even small in amount; (2) pain; (3) nausea; (4) pylorospasm of such persistence as to simulate pyloric stenosis; (5) inability to ingest comfortably the ordinary wholesome foods permitted by the circumstances of the patient, this making the poor patient a surgical case earlier than the well-to-do one; (6) inability to ingest comfortably enough food to maintain nutrition while living a normally occupied life; (7) recurrence after apparently a cure. Or, as C. H. Mayo expresses it: "The best type of gastric case for surgery is that in which every method of medical treatment has failed or the patients have become tired of the rigid diet and care which are necessary to relieve or to prevent relapse." This is our answer to the question when to operate in peptic ulcer cases. We shall not attempt to answer the question when to perform a second or a third operation if symptoms persist.

When an ulcer case is referred to the surgeon the physician must still feel his responsibility to the patient, and in order to provide against having a surgical failure follow the medical failure should urge the serious attention of the surgeon to the following statements, namely: that of Ginsburg, that "small quantities of food at frequent intervals have a better physiologic effect upon the recently short-circuited stomach than three daily meals;" that of Cannon, that "after gastro-enterostomy, effective action of the anastomosis demands that there shall not be more than a moderate distention of the stomach;" and that of Troell, that "the recurrence of symptoms following operation in many cases depends to a considerable degree on the surgeon's neglecting to give dietetic and other prescriptions suitable for ulcer." We would commend the counsel of W. J. Mayo that "following surgical intervention the patient should be under good medical advice until permanent cure is assured;" and that of Carter that "after operation every opportunity for healing and cicatrization should be given, involving, as this does, weeks or months, during all of which time the diet should be bland, soft and free from thermal, mechanical or chemical irritants." No longer should we tolerate a surgeon who places an ulcer case on heavy and bulky diet within two or three weeks of his operation.

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## THE PRINCIPLES UNDERLYING THE SAFE AND MORE RAPID EVOLUTION OF THORACIC SURGERY<sup>1</sup>

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MR. PRESIDENT, LADIES AND GENTLEMEN:

WHILE a dozen years ordinarily may represent an age in our times, they mean hardly more than a few months in medical science; and so, I hope, you will understand when I frankly state that, though I have all of eleven years to my credit in active clinical work as well as in the study of the literature on the subject, I consider myself no more than a mere tyro in thoracic surgery.

It took abdominal surgery fully forty years to develop to its splendid status, no small part of which was accomplished right here in Rochester. Nevertheless, every day, one might say, sees the great edifice of our abdominal work enlarged by some addition. It is true that thoracic surgery had the benefit of all the experiences gained in abdominal surgery as well as the additional asset of having started with a most perfect asepsis. But in spite of all this I hardly think we shall go much amiss in predicting that there will still remain problems to solve for our children and children's children.

Attention should be called briefly to the principal practical differences between abdominal and thoracic surgery. When we make an incision to reach a diseased organ within the abdominal cavity, *e. g.*, stomach, liver, appendix or what else it may be, if the anesthetist is efficient, the asepsis faultless, and we know how to do the required work, the majority of our patients recover. In the interval operation for appendicitis, for instance, we see of 100 patients 100 get well. When we cut into the abdomen, having divided the wall of this cavity and also the outer layer of the sac, which we call peritoneum, its contents lie before us in their anatomical relation as well as remain undisturbed until we disturb them; the respiration and the circulation of the blood, too, continue without disturbance. With perfect ease and equanimity we can go about our task. But in thoracic surgery the matter is not quite so simple. Granted the same perfection in every technical detail as before, every time a thorax is opened "something" happens that does not happen when the abdominal cavity is opened. It announces itself by a hissing sound. What is this something?

When we make an incision between two ribs, carefully separating layer after layer of muscular tissue, and at last also dividing the septum which we call the pleura, we open thereby the pleural sac

<sup>1</sup> Read before the Southern Minnesota Medical Association, Rochester, Minn., June 23, 1919.

which protects the lung. Under normal conditions the lung completely fills the space between mediastinum and chest wall, and the pleural sac surrounding it contains neither air nor fluid, excepting only a small amount of viscid, glue-like substance that permits the leaves of the pleura, the one covering the wall of the chest, mediastinum and diaphragm, the other covering the lung, to glide upon one another without perceptible friction, as two panes of glass do when there is a film of water between them. We have, then, under physiological conditions no air on the outside of the lung, but on the inside of the lung we find the pressure of the atmosphere, and this pressure keeps the elastic fibers, of which the lung tissue is largely built up, distended. This condition is changed through our incision which, being made for operative purposes, is usually a large one. The air has now free access to the space from which nature had it carefully excluded, and it is then that this "something" happens to which I have previously alluded: the large, freely expanding and contracting organ, the lung, that we had met upon opening the chest, suddenly leaves the inner chest wall, loses its contact with it and before our eyes becomes smaller and smaller until, no larger than a man's fist, it comes to rest near the spinal column. It has been put out of commission. The collapsed lobes no longer take part in the function of the lung of ventilating the blood, feeding it with oxygen and freeing it of the excess of carbon dioxide, and the space previously filled with the lung has become a large, empty cavity. Why does all this happen? It is due to the equalizing of air-pressure upon the inside and upon the outside of the lung. The one-sided air-pressure upon the inside only, which, as explained, kept the elastic fibers distended, being now counteracted by the equally great air-pressure admitted through our incision to the outside of the lung, leaves the contractile strength of the elastic fibers as the only active force present, and, unless the lung should happen to be adherent to the chest wall, it contracts down upon its pedicle, the bronchial tube, which enters it near the bifurcation of the trachea.

But that is not all. This is only what immediately follows the hissing noise of which I told you before. Something else happens. The thoracic cavity is divided in the center by a structure reaching from spine to sternum, which we call the mediastinum, with lung to the right and to the left of it, and in which are located the heart, the large bloodvessels connecting heart and lung, nerves and other soft tissues. From mere enumeration of these parts as the very seat of life itself, you will understand the importance of their being left undisturbed in their various functions. That, however, is just what is not the case after one side of the lung has collapsed. The patient makes strenuous efforts at breathing with the closed side of the lung and thereby sets the mediastinum in motion to the right and to the left, like a sail flops in a head-on breeze, which, like the mediastinum,



is fixed above and below. This to-and-fro motion of the mediastinum interferes with the proper ventilation of the still functioning part of the lung, and thus, though only one side is opened to the outer air, nevertheless both sides of the lung are injuriously affected. All this occurs only if the tissues within the chest are in their virgin condition. If in consequence of inflammation or other causes the soft mediastinal structures have become harder and more resistant it does not take place.

The condition just described is called pneumothorax, from the Greek "pneuma" = air, the term meaning: air in the thorax; it is unilateral or bilateral, according as to whether the outer air has direct access to one or both sides of the lung. The bilateral pneumothorax, unless promptly corrected, is always fatal; the unilateral is not always that. It seems that about 40 to 50 per cent. of patients are able to stand a unilateral pneumothorax; but, unfortunately, we have no means of knowing beforehand whom we may include in and whom we must exclude from this percentage. It is the same as in appendicitis, where the great majority of patients who have had one attack will have another sooner or later of which they may die. We cannot possibly know beforehand who will and who will not have a recurrence, therefore the rule that the inflamed appendix must be removed in every case, either during or soon after the first attack. It is a wise precaution. Along the same line of reasoning, if we know of a method to forestall pneumothorax, unilateral or bilateral, should we not apply it, thereby increasing the patient's chances of recovery? Surely, and more than that, it is our duty to do so. This method exists. This method consists in the use of apparatus designed to prevent the described effects of the inrush of air into the pleural cavity upon incision for operative purposes, and the general conditions here outlined as prevailing during the operation constitute the first principal difference between thoracic and abdominal surgery.

We now turn to the second principal difference between these two branches of surgery and find the same to pertain to conditions after the operation—to the after-treatment. Peritoneum as well as pleura tend to form adhesions after the operative wound has been closed, but the pleura has an additional tendency which the peritoneum has not equally outspoken. The pleura, being more sensitive to traumatism, discharges into the pleural cavity a fluid which we call an "exudate." Despite the most rigid asepsis this exudate does not always remain sterile, nor is it always absorbed. It may require drainage later on and may give rise to serious complications. A casual observer may here say: "Why not drain from the corner of the wound when closing up," or "Why not close the wound completely and drain through a lateral stab?" One thus arguing overlooks the air that would filter in alongside the tube, producing an "acute postoperative pneumothorax," which is no less

dangerous and often has the same fatal consequences as the above described acute operative pneumothorax.

Again I ask, would it not be a great step in advance if the danger of the postoperative pneumothorax could also be forestalled? If we could close up the thorax air-tight after the operation and yet drain? And this is the second point I want to bring out: We are able to do this. A method of air-tight drainage has been evolved which is safe and reliable and eliminates, barring an unforeseen accident, the danger of the occurrence of a postoperative pneumothorax.

I should be happy had I succeeded in holding your attention until now, but in the balance of my address I shall have to become more technical and address myself more to the medical men who good-naturedly have permitted me to explain to the ladies what to them is a matter of general knowledge.

I propose now to take up and discuss the two points before developed, viz., the prevention of the acute pneumothorax (collapse of the lung), during the operation and the prevention of the acute pneumothorax during drainage after the operation.

1. **Avoidance of the Acute Operative Pneumothorax.** The construction and use of apparatus for thoracic operations began in the middle of the 90's of the last century, when Quénu, of Paris, worked out an apparatus on the lines of a diver's helmet, in which the patient's head was placed under increased air-pressure together with a sponge saturated with chloroform. Tuffier, of Paris, soon after advocated and practised the use of insufflation of air into the trachea. They tested their suggestions by animal experiments which one of them, at least, followed up with thoracic operations on the human subject in the hospitals of Paris, avoiding the effects of an acute pneumothorax.

America, above all, has a right to be proud of the pioneer work she has rendered in this field. I am referring to the valve apparatus for artificial respiration worked out by Fell and to the pump apparatus constructed by Matas, of New Orleans, both designed on the basis of the O'Dwyer tube. In 1898, Parham, of New Orleans, made use of Matas's apparatus in a resection of the chest wall for tumor, the first recorded thoracic operation under differential pressure in this country. His patient recovered.

However, this case and similar ones remained isolated. They were interesting cases, and there it ended. More concerted action resulted when the differential pressure idea was conceived anew by F. Sauerbruch in 1903. He had been charged by his chief, the late Prof. v. Mickulicz, of Breslau, to find a method which would make work in the thorax as safe as that in other cavities of the body. The construction of Sauerbruch's negative chamber in the following year was the result of this work. Thus the year 1904 marks the real beginning of thoracic surgery by the transpleural route. The

apparatus designed for experimental work consisted of a box with the animal's head outside and the chest and body inside. A cut-out with rubber collar in one of the sides of the rectangular box served for the passage of the neck of the animal, surgeon and assistant sitting inside the box. The air-pressure in the box was reduced by machinery to a degree equalizing the force of the physiological force of contraction of the normal elastic lung tissue. This having been done, transpleural incisions could be made in the intercostal spaces right and left, or large flaps of the chest wall be raised, the animal continuing meanwhile to breathe as if nothing had happened. Upon reversing conditions the animal's head being put into the box and the body outside and the air-pressure within the box being increased, the same phenomenon, *i. e.*, non-collapse of the lung, was observed when the thorax was opened and the animal breathed the increased pressure.

On the basis of the artificial reduction of the air-pressure within the chamber below the normal atmospheric pressure, considering the latter as zero-pressure, this operative procedure was called "operation under negative pressure." The method as such was termed "operating under difference in air-pressure," or, briefly, "under differential pressure." In 1904 a large chamber, made of iron and glass, for operations on man was in use at Breslau.

Four years later an amplified type, constructed on the basis of Sauerbruch's principles, was built in New York and is now a part of the instrumentarium of the Thoracic Pavilion of the Lenox Hill Hospital of New York City. It is the only one in America.

The negative chamber represents an enlarged pleural cavity and is the most "physiological" apparatus in existence for complicated intrathoracic work upon weak and reduced patients. It permits of the use of differential pressure under general as well as local anesthesia. It is a splendid physical apparatus and will forever retain its scientific as well as its practical value. But the negative chamber is expensive and stationary, surgeon, assistants, nurses and patient have to go to the apparatus; the apparatus cannot be brought to the patient.

For this and other reasons the attention of the surgical world turned more to the positive differential pressure method, as first represented by the positive cabinet and its modifications. In quick succession three additional, useful procedures of employing positive air-pressure have been perfected: The mask method (1908); intratracheal insufflation (1910) and pharyngeal insufflation (1913). In each of them the lung is blown up artificially in order to overcome the pressure upon the outside of the lung of the atmospheric air, which communicates with the interior of the pleural sac by way of the incision.

The employment of any one of the four methods mentioned enables us to avoid the collapse of the lung on incising the pleural

cavity when adhesions between lung surface and chest wall are not present. In other words, any one of these four methods enables us to avoid the occurrence of the acute pneumothorax with its sequelæ and, therefore, makes work in the thorax perfectly safe.

In 1914 the opposition originally aroused by the differential pressure method as employed in thoracic operations had almost ceased. The method was recognized as safe for operative work within the chest by the great majority of colleagues interested in this branch of work.

In 1914 the war broke out and with it came a recrudescence of opposition.

Personally, I am fond of opposition, because opposition stimulates discussion and discussion is the foundation of progress. It was principally for the purpose of free discussion that the "American Association for Thoracic Surgery" was founded three years ago. But opposition must be constructive and not destructive. In this particular instance the opposition, to my mind, is decidedly destructive.

When the war came many of the men who went overseas were suddenly confronted with important traumatic chest cases and were compelled to do chest surgery without previous practical experience in this line. After temporizing for a time, they became aggressive, opened the injured chest widely, did the required work as in other parts of the body, closing the thorax as they were accustomed to closing the abdomen and saw splendid results, though no differential pressure apparatus had been used. No wonder they became enthusiastic and soon proclaimed: "There is no fundamental difference between operation within the abdominal and thoracic cavities; differential pressure is an unnecessary ballast; we can well get along without it." And, in order to carry his point, one renowned colleague even suggests the division of thoracic surgery into different chapters, requiring different types of operation, *e. g.*, lung surgery and esophageal surgery.

How can we explain the discrepancy between the experience in thoracic operations at or near the front and as seen in peace practice at home?

It has been stated on the basis of investigations made during the war that 50 per cent. or more of the patients with penetrating chest wounds died on the battle field. Those who reached a hospital behind the lines were the ones who had not succumbed to the effect of the acute pneumothorax and hemothorax, *viz.*, the sudden entrance of air plus blood into the chest. Let us remember, further, that these soldiers were young men in the prime of life, who had not been sick for months and years, as is the case with the majority of patients whom we are called upon to treat for thoracic disease in times of peace. On these young and strong men, who had survived all the immediate consequences of the injury of the chest, our colleagues

who were abroad were called upon to operate; on these they gathered their experience. Under aseptic precautions they made an incision of the required length—and the long chest wound usually is better for the wounded than a small one, which latter often permits air to enter the chest, but not to leave it readily—pulled the lung forward and held it in front of the wound for the necessary work. The mediastinum now could not flop from one side to the other, the well-known method to avoid the development of the symptoms of the acute pneumothorax (Müller's trick). The mediastinum is thus steadied during the operation and the lung is attended to as the case may require and then dropped back. If the chest was closed airtight the great majority of patients had a good chance of recovery and were seen to recover.

With this impression in mind, renowned medical men have come from England, France and Italy in the course of the last three years to visit us. They have travelled through our country and have given us the results of their personal experiences. Some of them had been carried away by the favorable results obtained in traumatic chest surgery, done without any apparatus, on soldiers who had survived the shock and the effect of acute pneumo- and hemothorax, done while the soldiers were still suffering from them, and they wondered why any surgeon had ever thought it necessary to make special provision for an interference in the interior of the chest.

I have the greatest admiration for their medical courage, to take up under such adverse circumstances a new line of operative work and, what is more, make a success of it. All honor to them!

On the other hand, I cannot help asking is it right to draw such sweeping conclusions from the experience in one small part of the surgery of the chest—the traumatic—with reference to thoracic surgery in its entirety? To my mind it is not permissible.

To show how discussion helps in clearing up a fundamental question like the one we are considering allow me to cite a personal experience: When the commission of surgeons from the front, consisting of three representatives from England, one from France and one from Italy, came to attend the American Congress of Surgeons in October, 1918, they visited the Lenox Hill Hospital of New York City and looked over the thoracic apparatus there installed. After a heart-to-heart talk of almost two hours on the means at hand today, to avoid or overcome the acute pneumothorax in chest operations, three of the five gentlemen joined me in the stand: that we do need the differential pressure method for safe operating within the thorax.

I most fervently hope that those colleagues who still think differently, because they have had favorable experiences in chest surgery without the employment of apparatus, will come forward and relate their observations. If their charts prove that the work can be done equally well and equally safely for the patient, without

apparatus, why should we trouble ourselves with differential pressure methods? why should we not throw all apparatus overboard and proceed as in other parts of the body? I for one still believe that if we had one hundred patients with surgical chest disease and gave fifty cases each to two surgeons who commanded equally good technic and perfect asepsis, one working with apparatus and maintaining the physiological working of the lung during the operation, the other one working without apparatus, I say, I feel sure, that the one who used the differential pressure method would get a higher percentage of recoveries than the one who did not use it.

2. **Avoidance of the Acute Postoperative Pneumothorax and of the Accumulation of the Pleural Exudate by Means of Air-Tight Thoracic Drainage.** In my endeavors to drain the chest and, incidentally, to avoid the occurrence of the acute postoperative pneumothorax I have at last decided upon a method of choice. It is an adaptation to general operative work of the method of air-tight drainage used by Dr. Kenyon, of New York City, in the treatment of empyema in children, and practised in a similar way, for the treatment of the same disease in patients of any age, by Buelau, more than twenty-five years ago. I consider it a universally useful method for draining the chest air-tight, after any and every kind of intrathoracic work. To keep the patient with free (not air-tight), thoracic drainage under the influence of differential pressure within the apparatus, negative chamber or positive cabinet, as worked out at our hospital six or seven years ago, is also an excellent method, but it is cumbersome.

Of another evidently useful method, Tiegel's metal drain, with valve arrangement at its outer end, I have no personal experience.

Today, before closing the chest incision completely by layer sutures, we make a stab one or two interspaces lower in the posterior axillary line, introduce in air-tight fashion a rubber tube about as large as the third finger of a man, the tube having one or more side holes near its inner end and outside a short glass tube interposed, fasten it securely with broad adhesive plaster strips and let its free end dip into a graduated siphon bottle, which is partially filled with sterile water or some kind of antiseptic solution. Our observations and results have shown this to be a splendid and reliable method for accomplishing our purposes. One can see in the glass tube the quality of the secretion and measure in the siphon the quantity discharged within a given period. At the same time this method thoroughly and safely fulfils the demand made by those most experienced in thoracic surgery: to always close the chest air-tight in order to allow the lung to expand at once.

The two principles underlying the safe and more rapid evolution of thoracic surgery, as I see them, then, are:

1. The use of the differential pressure method in order to avoid the occurrence of an acute pneumothorax during operation.

2. The immediate and complete closure of the incision in conjunction with air-tight thoracic drainage after every case of thoracic operation in order to avoid the acute postoperative pneumothorax as well as the accumulation of exuding fluid within the pleural sac.

(A series of lantern slides then illustrated the points previously discussed.)

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## SURGICAL TREATMENT OF PLEURISY.\*

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PROGRESS in the operative treatment of pleuritic effusions has until recently, been impeded by the concentration of surgical attention upon the curative therapy of empyema. This is an important part of the problem, but only a part, as purulent pleurisy is merely the late stage of some of these affections. The first therapeutic advance, made about five centuries B.C., was the conversion of a closed into an open pyothorax to start drainage. The second notable step forward, taken some twenty-four centuries later, was the conversion of an open pyothorax into a closed thorax to stop drainage. A third line of progress, starting with this latter period, has developed a method of air-tight drainage whereby both prophylactic and curative measures can find their simplest application.

Open thoracic drainage was introduced by Hippocrates, who recognized that simple acute, fetid or chronic empyema could be idiopathic, traumatic, postpneumonic or precede or follow phthisis. He learned that the drain should be placed low and that open drainage should neither be established too early nor be permitted to proceed too rapidly. Twenty-four hundred years' experience and observation have added very little to these teachings.

Closure of an open pyothorax has always been a serious problem because a proportion of individuals fail to heal spontaneously after thoracostomy. No doubt Hippocrates was confronted with the identical dilemma of a death from amyloid disease, an operative failure or considerable physical and functional disability. There are but three ways healing can be fostered under these conditions: (1) By collapsing the thoracic parietes against the retracted lung through some form of costoplasty, a method with which the names of Estlander and Schede are associated; (2) by releasing the adhesions surrounding the collapsed lung, the principle of decortication of Delorme and thereafter expanding the lung to meet the parietes; (3) by obliterating the intrapleural space with tissue transplants or

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by the introduction of some form of synthetic filling compound into this cavity in an attempt to obtain ultimate repair. Each of these methods implies a means of securing adequate tissue disinfection, *e. g.*, excision, lavage, chemical action.

H. I. Bowditch,<sup>1</sup> of Boston, began in 1850 to aspirate and to reaspirate in the treatment of pleuritic effusions. He proved that such treatment was efficacious in combating pleurisy as well as in preventing and in curing empyema. This celebrated internist must be given great credit for having demonstrated the wisdom of treating pleurisy by early air-tight, one-way drainage.

The foregoing summary includes the methods essential in treating pleurisy if applied so as to cooperate with natural defensive reactions. Pleural resistance is highest when pleural surfaces are in apposition.<sup>2</sup> Such apposition can be maintained or reestablished only when there is adequate pulmonary inflation. Pleuritic effusions are produced more rapidly than they are absorbed, and if they are not removed pulmonary deflation and pleural separation are inevitable. Drainage is therefore positively indicated in the early treatment of pleurisy, and it must be air-tight, one-way drainage or pulmonary deflation and pleural separation are again assured.

There is now available an abundance of evidence exemplified in the reports of Whittemore<sup>3</sup> and McKenna<sup>4</sup> to prove that results obtainable by this method of drainage treatment are superior to any yet recorded when the immediate mortality and the duration of convalescence are considered. In addition there is a more nearly perfect restitution of health through the preservation of the tripod upon which functional integrity of respiration depends, namely, free mobility of the thoracic parietes, normal intrapleural negative pressure and unimpaired pulmonary elasticity.

Air-tight, one-way drainage, whether employed interruptedly by aspiration or constantly as a catheter drain inserted through a rib or between ribs, or as a rigid tube sewed into a defect produced by rib resection, has been proved efficacious in controlling traumatic pleurisy, including the type following thoracotomy,<sup>5</sup> in reducing the irritations of acute simple pleurisy and in promoting recovery from empyema either with and without lavage. To this list I can add the control of encapsulated (interlobar) empyema and of tuberculous and carcinomatous pleuritic effusions.

This simple drainage is, however, not a panacea. It will reduce the number of major operations and minimize the severity of those which cannot be avoided, provided it is properly used. The method advocated consists in intercostal insertions by means of a trocar

<sup>1</sup> Boston Med. and Surg. Jour., 1884, cxi, 572.

<sup>2</sup> Yates, J. L.: Annals of Surgery, 1920, lxxi, 241.

<sup>3</sup> Boston Med. and Surg. Jour., 1919, clxxxi, 575.

<sup>4</sup> Bulletin of Chicago Medical Society, 1920, xix, 22.

<sup>5</sup> Laboratory of Surgical Research, A. E. F., Boston Med. and Surg. Jour., 1919, clxxx, 405.



of one or more 16 F. catheters, provided with check valves, at the most favorable level for drainage (and lavage) compatible with the patient's comfort, which is determined by possible limits of activity, by whether the individual be bedridden in one position or is able to sit up or even to walk. The force required to expel the exudate, reestablish normal negative pressure and pulmonary inflation is furnished by the increased intrathoracic pressure of deep inspiration. No strong suction is required though a constant slight negative pressure is often essential to prevent the serous exudate from coagulating within the drainage tube. The tip of the catheter should be introduced far enough to function but not far enough to make avoidable contact with the expanding lung. Such an introduction can be made accurately only with fluoroscopic control. The insertion is done under local anesthesia after so dislocating the skin that when the catheter is withdrawn, the skin in resuming its normal position acts like a check valve in closing the drain track. If drainage be required for more than a week the tubes must be then removed and reinserted at another point or there will be danger of air leakage around the tube, a danger which becomes a certainty a few days later.

If the tubes are improperly inserted through the skin, at the wrong level or to too great extent and allowed to remain overlong in one position, all of the conceivable misfortunes connected with the most disastrous complications of both closed and open pyothorax can develop. In addition the insertion of a trocar uncontrolled by a fluoroscope can wound the diaphragm, the lung or even the pericardium. Irrigations, if attempted too early, can disseminate infection or break down limiting adhesions. If given too forcefully they can cause similar catastrophes or lead to dangerously violent paroxysms of coughing or choking, particularly when the first lavage is not done with salt solution and Dakin's solution is too irritating. This is certain to be the case if a bronchial fistula is present.

The invaluable lessons come from failures. The blunders above enumerated have been observed. In a group of empyema patients treated improperly by simple drainage the mortality rate and the proportion of serious complications, especially open pyothorax with a firmly contracted lung, were much higher than they would have been had routine Hippocratic open drainage been employed. It is fair to assert that if principles are given proper attention methods will take care of themselves. This is true providing the gross folly of being principle-wise and procedure-foolish is avoided.

Quoting from Bowditch: "It (aspiration) has been of infinite service to mankind and will ever continue to be such. It will save lives which without it will be lost. All that is required is that due care govern the use of it."

# CAN THE GALL-BLADDER, BILIARY DUCTS AND LIVER BE MEDICALLY DRAINED?

A FURTHER CONSIDERATION OF SOME ASPECTS OF DIAGNOSIS AND  
TREATMENT OF CHOLECYSTITIS AND CHOLEDOCHITIS BY A  
METHOD OF PHYSIOLOGIC DRAINAGE. THIS IS  
THE FIFTH OF A SERIES OF PAPERS ON  
THE GALL-BLADDER.<sup>1</sup>

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In a previous paper<sup>2</sup> I called attention to a direct, non-surgical method of draining the biliary apparatus. In that paper I mentioned the fact that the experimental observations on dogs by Meltzer<sup>3</sup> aroused my curiosity and created the desire to extend those experimental studies to human beings.

As a prelude to your understanding the principles underlying this method of non-surgical drainage, you must know that Meltzer found that when he directly douched the duodenum with a solution of magnesium sulphate he could cause "a completely local relaxation of the intestinal wall," and that this relaxing effect was not observed when this salt was administered by mouth and allowed to pass across the gastric mucosa before it reached the duodenum. Meltzer then suggested testing, by means of the duodenal tube, in jaundice and in biliary colic, the local application of a 25 per cent. solution of magnesium sulphate. "It may," he says, "relax the sphincter of the common duct and permit the ejection of bile, and, perhaps, even permit the removal of a calculus of moderate size wedged in the duct in front of the papilla of Vater."

This very interesting observation of Meltzer's, although mentioned in an inconspicuous footnote, seemed to be pregnant with much practical importance. His paper was published in April, 1917, and that same month I began my first clinical experimental observations on human beings by means of the duodenal tube and various solutions of epsom salts and other substances. During the past thirty-two months I have made over 1200 biliary taps on 121 different patients,<sup>4</sup> both for diagnosis and treatment, and I have

<sup>1</sup> Read before the Section of Practice of Medicine, College of Physicians, Philadelphia, Pa., January 26, 1920, and Academy of Medicine, Cincinnati, Ohio, February 2, 1920.

<sup>2</sup> Reprinted from the Journal of the American Medical Association, September 27, 1919, lxxiii, 980-982.

<sup>3</sup> AM. JOUR. MED. SC., April, 1917, cliii, 469.

<sup>4</sup> Since the presentation of this paper in January, 1920, to date of publication, the total number of cases studied by this method has reached 309, with a total number of biliary drainages of 2240.

become more and more convinced of the practical ease with which both the normal and the pathologic biliary apparatus can be drained of its contents, with certain exceptions and within certain limitations, to which I shall refer later on. Further than this, I believe it possible to segregate and study bile obtained from the duodenum, from the bile ducts, from the gall-bladder and from the liver. I do not mean you to infer that this segregation of bile can be made so sharply that it can be said positively that any given sample is derived *exclusively* from the bile ducts or from the gall-bladder or from the liver, but segregated to the extent that it is possible to infer that the *larger amount* of the various types of bile recovered during a biliary tap is being drained from the ducts, from the gall-bladder or from the liver. If this much is admissible I believe it possible by cytologic, cultural and chemical studies of these various portions of segregated bile to make certain inferential diagnostic deductions as to the condition of health—physiologic or otherwise—or disease within those ducts, that gall-bladder or that liver.

In my first paper I attempted briefly to classify the types of bile thus segregated from cases of choledochitis, cholangitis, cholecystitis and cholelithiasis on the basis of their cytology, bacteriology, chemistry and their gross appearance. The interest with which that paper has been received in various parts of the world has encouraged me to present further observations of diagnosis and treatment by this method and to include a few case reports.

In presenting these observations I shall endeavor to record the phenomena which I have seen, to try to separate facts from theories and to hope to correctly interpret these facts and to substantiate these theories. Although I admit that personally I have arrived at certain very attractive conclusions from my studies I shall endeavor to refrain from stating them, because I realize that conclusions, especially if premature, often take on the undesirable characteristics of the boomerang.

For a clear understanding of what will follow in this paper it will be necessary to briefly allude to the anatomy, histology and physiology of the biliary system, which consists of the liver, the gall-bladder and the bile ducts. For the purposes of this paper I can describe the anatomy of the biliary system in a somewhat primer-book fashion as follows: The liver, the largest of the digestive glands of the body, is an organ whose substance is made up of myriads of bile-secreting polyhedral cells and certain stellate cells (Kupffer) arranged in the form of a lobule. Each lobule is supplied with blood coming from the portal vein and from the hepatic artery. In the portal vein the blood carries soluble substances absorbed from the intestines, certain of them useful substances, such as the various glucoses and proteids, which are reabsorbed by the liver for further use, and certain waste products drained from the organs emptying into the portal vein and which the liver must excrete. The hepatic artery brings to the liver cells themselves their daily

pabulum, which permits them to carry on their function of absorption and secretion. Each lobule, too, is furnished with a rather complicated network of vascular and bile capillaries, but for my purpose it is enough to recall the fact that the bile capillaries run in minute grooves or canals between the trabecular-like tubules of liver cells, which they drain and empty the bile into the interlobular bile ducts. These interlobular ducts are collected in larger channels, which in turn carry the bile into the right and left hepatic ducts and thence out of the liver. The lymphatics and nerves to the liver follow somewhat the same general arrangement. The liver, therefore, has three principal functions: absorption, secretion, and excretion. It absorbs from the portal blood soluble products from the intestinal tract—notably sugar, proteid, bile salts and pigment—which are acted upon by the metabolism of the liver cells before being stored up in the liver or passed back again into the general (blood or bile) circulation. It secretes a fluid substance called bile, which is of great aid to proper digestion, particularly acting as a co-partner with the pancreas in the absorption and digestion of fats. By means of the bile it excretes waste products and bacteria brought to it by the portal blood and probably by means of metabolic activity of the liver cells filters out, or neutralizes, toxins, both chemical and bacterial. The bile is carried from the liver by the right and left hepatic ducts, which soon unite into a larger one, and are joined by the cystic duct, and their union forms a larger (or common bile) duct, which empties the bile into the very beginning of the intestinal tract. These efferent bile ducts are lined by columnar epithelium varying in height according to the caliber of the duct. The larger ducts are supplied with unstriped muscle fibers, chiefly longitudinal, and small mucous glands. At the terminal portion of the common bile duct, in that portion that runs obliquely between the coats of the duodenum, this unstriped muscle becomes augmented into a definite circular bundle, which Oddi described, and which acts as a sphincter controlling the expulsion of bile into the intestine. Connecting with the cystic duct is a pear-shaped, distensible sac, the gall-bladder, which is composed of an outer coat of fibrous elastic tissue, a muscular coat, largely composed of circular bundles of unstriped muscle fibers, and a mucous coat covered with a single layer of columnar epithelium and thrown up into a network of slightly raised ridges that give the mucosa a reticulated appearance. At the neck of the gall-bladder may be found branched mucous glands.

That the gall-bladder has a function has recently been disputed, especially by surgeons, but if it has a function—and I, for one, believe it has—it primarily consists of acting as a reservoir for the bile secreted by the liver, which dripping down the bile ducts encounters a closed sphincter, and which has no outlet except to dam back through the cystic duct and into the gall-bladder. Here it remains stored for a variable time, becoming more concentrated,

until physiologically the sphincter of the common duct is relaxed, as a spurt of gastric chyme enters the duodenum; then bile is poured into the intestine in quantities suitable to the needs of the elements in the food to be digested, and here is where the secondary role of the gall-bladder function comes into effect. It is a well-known fact that a gastric chyme rich in fats, proteoses and peptones, partly because the bile aids in their direct digestion and partly for other reasons, as it passes the duodenal mucosa stimulates an excessive amount of excretion of bile. This then the healthy gall-bladder is able to furnish in concentrated form and appropriate dosage, whereas a diet rich in carbohydrate in whose digestion the action of bile is less concerned does not cause as copious excretion of bile; but the carbohydrates need pancreatic juice, which is delivered through the relaxed common duct sphincter together with such quantities of bile as may lie in the ducts. In this type of diet it is altogether likely that the gall-bladder does not play such a prominent part.

Prolonged periods of quiescence on the part of the gall-bladder—waiting for its physiological stimulus of fats or end-protein-products of gastric digestion—should logically predispose to biliary stasis.

It would be interesting to ascertain the relative frequency of functional (?) biliary stasis and later biliary disease occurring in people who have adopted a vegetarian dietary. This would help to settle the question. Similarly, it would be interesting to learn the liability to biliary stasis and gall-bladder disease occurring in men who for some years have worked under pressure, and have either missed the noonday meal or have hastily eaten a piece of pie or shredded wheat biscuit and glass of milk—a characteristic lunch of the busy business man or doctor during his foolish formative years. I can think of several such doctors who are today minus their gall-bladders.

Now let me pick up some of the loose ends and partly recapitulate. We see that physiologically the biliary system consists of an organ (the liver) which is probably constantly secreting bile, but is excreting it intermittently into the intestines. The function of excretion is controlled by the physiologic opening and closing of the sphincter which guards the outlet of the bile-conducting tubes. When this sphincter is closed it is probable that the secretion of the liver slows down somewhat, but it is also most probable it does not cease altogether and that the bile secreted passes down the ducts to find the sphincter closed, and having no other outlet the excess bile dams back into the gall-bladder—which has wisely been placed in the proper position to act as a reservoir for such an overflow. Is it not probable that the gall-bladder has been provided with an outer fibro-elastic coat to permit of variable degrees of distensibility? It is true that the velocity or rate of liver secretion varies in response to substances brought to it in the blood (and possibly through nervous influences), for Bayliss and Starling have demon-

strated that an acid gastric chyme on reaching the duodenum activates prosecretin into secretin, which is carried to the liver by the blood and stimulates its secretory activity, in a similar way in which these same hormones influence pancreatic secretion. It is my opinion that there may be a hormonal influence that passes to the gall-bladder itself which, independently perhaps of that inducing increased velocity of liver secretion, causes the gall-bladder to contract and deliver various amounts of its concentrated bile, and that this selective hormonal influence may lie in the *food chemistry* (proteoses and peptones) of the acid gastric chyme. For I, as doubtless many other observers, have been impressed with the inferential diagnostic importance, in patients with the biliary syndrome, of the low subacid or anacid fractional gastric curve, as pointing to biliary stasis with cholelithiasis rather than to cholecystitis alone. In my experience the cases of cholecystitis are more liable to show a normal or hyperacid fractional curve not unlike that seen in the majority groupings of duodenal ulcer and chronic appendicitis with reflex gastric symptomatology.

Now upon what does the mechanism of emptying, partially or wholly, this biliary system, depend? We can look for the answer to this by examining into the nerve supply of the duct sphincter and of the gall-bladder.

Doyen has specially studied the innervation of the gall-bladder, and his experiments were confirmed and amplified later by Freese. Both have shown that the gall-bladder receives both motor and inhibitory fibers by way of the splanchnic nerves, which emerge from the spinal cord in the roots of the sixth thoracic to first lumbar and pass to the celiac plexus.

Sensory fibers capable of causing a reflex constriction or dilatation of the gall-bladder are found in both the vagus and the splanchnic nerves, and it is found that stimulation of the (a) central end of the cut splanchnic causes a dilatation of the gall-bladder (reflex stimulation of inhibitory fibers); (b) central end of vagus causes a contraction of gall-bladder, dilatation (inhibition) of the duct sphincter. It is probable that the afferent fibers run in the vagus.

*Conversely*, stimulation of the peripheral end of the splanchnic nerves in the duodenum and the common bile duct causes simultaneously a relaxation of the tonus of the duct sphincter and a contraction of the gall-bladder.

Thus we find a double innervation of antagonistic or crossed action, which Meltzer calls "contrary innervation," and around which he has formulated a "law of contrary innervation," which he not only applies to emptying the gall-bladder but which he finds holds true for many functions of the animal body.

Meltzer draws an analogy between the biliary and the renal system. The latter is made up of a constantly secreting organ, the kidney, passing its secretion down a series of tubes guarded at their outlet by a sphincter muscle with a distensible sac, the urinary

bladder, placed between the two. Owing to the double and contrary innervation of this system, when we wish to empty the bladder we contract the detrusor muscle of the bladder and inhibit the tone of the sphincter urinæ, and when the urine has been expelled the process is reversed, the sphincter contracts and the detrusor muscle becomes relaxed until sufficient kidney secretion has accumulated to fill or partially fill the bladder again when the act is repeated. This, of course, in health is a voluntary action, whereas the emptying of the biliary system is entirely independent of the will—otherwise the analogy is complete. Would that we were given a consciousness of an overdistended but otherwise healthy gall-bladder and could empty it when we wished, for then many of the diseased states of the gall-bladder, which we are now called upon to diagnose and to treat would be forestalled. But Nature has left the solution of this secret for our present and future endeavors. Possibly we are nearer the threshold of discovery than we think.

Now to make my hypothesis more understandable let me quote from Meltzer's article at some length. He says:

"While the physiologic muscular and nervous mechanism of bile storage and bile discharge is thus satisfactorily explained, the question presents itself: What are the causes that bring about either of the two actions? We compared the mechanism of the gall-bladder with that of the urinary bladder. But the latter is to a large degree under the management of the will, and the sensation of fulness and other sensory stimuli bring the condition of the bladder to the attention of our consciousness, which, by means of the will, sets the required part of the mechanism into action. The processes of storing of the bile or of emptying it never comes to our consciousness and are never managed by our will. What does then manage their proper activity? We must admit that we do not yet know a great deal about it. It is probable that certain conditions and certain substances exert a selective action upon the reciprocal reflexes. It is interesting to quote here some newer instructive statements. One comes from Pavlov's school. Bruns stated that no bile appeared in the duodenum as long as the stomach is empty—when a meal is taken the entrance of chyme into the duodenum gives the signal for an ejection of bile from the common duct. Most interesting are the recent studies of Rost. He first established the fact that after *cholecystotomy* the escape of bile through the papilla of Vater is indeed continuous, while in normal animals it is a discontinuous one, depending upon the entrance of food into the duodenum. He found, further, the instructive fact that injection of peptone or albumosis through a duodenal fistula in a normal dog causes immediately a discharge of bile from the common duct, and he has proved that this takes place by a reflex act which causes a contraction of the gall-bladder and simultaneously a relaxation of the sphincter of the common duct.

"From the foregoing it seems quite safely established that the

physiologic discontinuous character of the flow of bile into the duodenum is regulated by a reflex mechanism, dominated by the law of contrary innervation; that the integrity of the gall-bladder is an important part in this reflex mechanism; that the discharge of bile can be greatly curtailed by the absence or a restriction of the discharge of chyme from the stomach into the duodenum and that the discharge of bile through the papilla of Vater into the duodenum is greatly enhanced by the presence in the lumen of the latter of peptone or albumosis."

It is probably beyond controversy to say that the physiologic mechanism of the storage and discharge of bile is a reflex mechanism. It remains for the future to decide how much of it is a direct reflex (gastric chymes, etc.) and how much indirect, due to hormonal action. It is certain that both of these factors, and possibly others, enter into the complete physiologic mechanism.

Now, then, the hypothesis upon which I have been working frames itself around the fact that Meltzer (reinforced by the observations of Rost) found that by douching the duodenum *locally* with magnesium sulphate he could relax the duodenal wall and probably with it the sphincter of the common bile duct. This was all he said, but arguing from cause to effect it seemed evident that if his law of contrary innervation were a sound one, when the sphincter was inhibited the gall-bladder should be stimulated to contract and should empty its contents (wholly or in part) into the duodenum, and by means of the duodenal tube the bile could be collected into bottles for study. This was by no means difficult to verify, and after a few observations the practical possibilities of this very simple method of examining into the diagnosis of many of the biliary diseases was quickly seen. And later, as I have gone on with my observations, there has dawned on me a very attractive vista of future possibilities, particularly in regard to treatment by this method if only I can "get it across" to the profession in general, and if I can stimulate others to study into its practicability.

And now I have come to a point in my paper where, with this preliminary understanding of the question I am discussing, I can again put on record the observations which I published in my earlier papers<sup>5 6 7 8</sup> on this subject and to which I will ask you to refer for the details that time does not now permit me to enter into. And without coming to definite or hasty conclusions myself, I will ask you to examine carefully the sequence of findings in a non-surgical gall-bladder tap and by your critical discussion of them help to put a correct interpretation upon their meaning.

When a duodenal tube is passed through the pylorus of the stomach, during its interdigesting or fasting period, it should find

<sup>4</sup> Lyon: Jour. Am. Med. Assn., September 27, 1919, lxxiii, 980.

<sup>6</sup> Lyon: AM. JOUR. MED. SC., April, 1920, clix, 503.

<sup>7</sup> Lyon: Med. Clinics of North America, March, 1920, iii, 1253.

<sup>8</sup> Lyon: New York Med. Jour., July, 1920, Nos. 1 and 2, cxii, 23 and 56.



in states of health the sphincter of the bile duct closed and the duodenum free of bile; but within a few minutes after irrigating the duodenal mucosa with a solution of magnesium sulphate of various strengths it will be possible by either gravity drainage or by gentle vacuum suction to recover bile, indicating that the tone of the sphincter of the common duct has been inhibited, its walls relaxed and that by the *vis á tergo* in the biliary apparatus the bile is being forced into the duodenum.

There should be little argument over the statement of my belief that the first bile collectable should be coming from that lying within the ducts themselves, and especially of the common duct, since it is obviously the first source of supply. To relax the common duct I have for the most part used a solution of magnesium sulphate varying from 12.5 per cent. to 50 per cent. of a saturated solution in amounts between 50 to 100 mls. It has seemed to me that the stronger solutions of 25 to 37.5 per cent. have given an optimum amount of sphincter relaxation which lasts from a period of one to two hours. Through the glass window cannula placed about eight inches from the proximal end of the tube can be observed the changes in color, viscosity and gross abnormal elements in the bile being recovered and which can be received into separate receptacles for differential study by attaching sterile vacuum bottles.

The first bile collected is usually diluted with a few milliliters of the magnesium sulphate solution, but its color gradually deepens until it becomes apparently a pure bile of a light golden-yellow color and of medium viscosity, like that of syrup, and in healthy bile ducts perfectly transparent (with a certain exception to be mentioned later). After a few milliliters of this bile have been withdrawn (which varies, perhaps, from 10 to 30 mls.) the bile suddenly deepens to a considerably darker golden yellow and becomes noticeably more viscid, and usually transparent in healthy states, draining sometimes steadily, sometimes with slight intermittency until amounts have been recovered which have varied from 30 to 166 mls., within my personal observations, when a sudden transition in color and viscosity of the bile again appears, this time to a light transparent lemon yellow and distinctly thinner and more limpid than either of the former types, and this type of bile continues to flow with considerably greater intermittency as long as the relaxation of the common duct sphincter is maintained; the amount of this last type of bile recovered has varied from a few milliliters to several ounces. Now I will ask you the question, Where is this darker colored bile in the amounts of from one to five and a half ounces coming from? It is my personal belief that it is coming from the gall-bladder wholly or in part, but mixed, probably, with a few milliliters of bile still delivered from the ducts or bile freshly secreted from the liver. This is really the central point of this paper. Is this darker colored bile coming from the gall-bladder?

My reasons for believing it is derived in large part from the gall-bladder itself are four:

1. Because I believe that Meltzer's law of contrary innervation as applied to the biliary apparatus is a correct one and is based upon a sensible interpretation of the most probable mechanism of the physiological storage and discharge of bile, supported by the experimental observations already recited, and which I have had opportunity to confirm by my clinical experimental studies. Now, if this law of contrary innervation as applied to the biliary system is a tenable one, and if the action of magnesium sulphate serves to relax the tonus of the sphincter of the duct, then it must also serve to contract the gall-bladder walls and cause it to expel its contents, wholly or in part, depending on the one hand on the tonicity possessed by any given gall-bladder wall and upon whether its cystic duct is patulous, and on the other hand upon the length of time in which the impulse to gall-bladder contraction and sphincter relaxation continues to be maintained.

2. My second reason lies in the fact that the color and viscosity of this second bile indicates a higher concentration and strongly suggests it as coming from its storage chamber within the gall-bladder; that in certain pathological cases (cholecystitis and high grade biliary stasis) this bile is a thick, sometimes almost tarry, greenish-black, of the consistency that we have all of us seen scooped out of the operated gall-bladder; that its cytology in health, but far oftener in diseased states, shows a larger amount of desquamated columnar epithelial cells deeply bile-stained, as if they had lain in contact with concentrated bile for some time. On occasions I have recovered bile-stained columnar epithelium in such massed abundance that they gave a ridged appearance, such as the reticulated folds of the gall-bladder mucosa possesses. Furthermore, in cases of clinically suspected cholecystitis it is in this second bile that appear by far the larger number of mucopurulent flakes, rich in pus cells and inflammatory debris and often swarming with bacteria, and lastly because the microscopy of this second bile finds normally the larger deposition of bile crystals. In several calculi cases that have been operatively (or otherwise) confirmed, bile crystals occurred in such abundance as to give a gritty or sandy feel to the bile when rubbed with the finger. This observation, together with one other that I shall mention later, offers the most practical differential inference as to the presence of potential or present cholelithiasis.

3. My third reason for believing that this second bile is derived largely from the gall-bladder lies in the fact that unless we account for it as gall-bladder bile we must account for the presence of from one to (in certain cases) nearly six ounces of this darker colored and more concentrated bile as coming from somewhere between the common duct sphincter and the secreting cells of the liver. Now, how much bile do you suppose the common and hepatic ducts can contain in their total length of  $8\frac{1}{4}$  inches and their average diameter of  $\frac{1}{4}$  inch? Surely it is unlikely that they could hold 90 to 150 mls.

At any rate, if this second bile is *not* from the gall-bladder the burden of proof will rest with the opponents to my theory as to whence it is derived.

4. My fourth reason, and I feel it is the strongest, for believing that this second type of darker yellow and more viscid bile is actually coming in large part from the gall-bladder lies in this (I think) convincing fact, namely, that in the cholecystectomized patients that I have studied postoperatively, some ten or more cases, I find, (a) that I never recover the second type of dark bile<sup>9</sup> but pass immediately from the light golden yellow or relatively more concentrated common duct bile to the light lemon yellow and limpid bile that I believe is freshly secreted liver bile and collectable for long periods as rapidly as it is secreted, and (b) I find that (in this cholecystectomized group) in the larger number of instances bile is continuously entering the duodenum in the fasting stomach and duodenal state, indicating that the duct sphincter is in a state of inhibited tonus, probably permanently so, since the antagonistic or contrary innervation has been cut when the gall-bladder was removed.

5. I might add a fifth reason, to the effect that in my post-operative group of cholecystostomized patients upon whom this non-surgical method has been practised (because the length of time over which surgical drainage could be maintained has not been sufficient to allay the catarrhal inflammation or to arrest the infection), that is in this group, together with a group of non-operated patients with cholecystitis or with gall-bladder biliary stasis, I have seen this second type bile, easily demonstrable as pathologic, gradually clear up and return to a more normal appearance under biweekly drainage by this method.

A little while ago, I made the statement that within my observations I find the bile, always in states of health, and indeed in certain states of disease (*e. g.*, infective cholecystitis of low grade without producing a recognizable catarrhal inflammation, and in certain types of biliary stasis) of a transparently clear yellow color with one exception. This exception occurs when a spurt of gastric acid juice enters the duodenum and mixes with the bile being collected, when an instantaneous turbidity is produced, the microscopy of which reveals a precipitate (?) of lecithin, neutral fats, mucin and occasionally other elements which, as yet, I have not identified. The density of this turbidity varies apparently in direct proportion to the concentration of gastric acidity. It can be artificially produced in almost every specimen of bile by adding to it a few drops of dilute hydrochloric acid, a 0.5 per cent. solution causing a very dense turbidity.

<sup>9</sup> It is conceivable that in cases in which the gall-bladder has been removed, and in which the ducts remain infected and the common duct becomes secondarily obstructed, that in such cases dark, inspissated or static bile might be recoverable.

I wish, too, at this point to state the second observation that may help in the differential diagnosis of cholelithiasis by direct study of the bile (in addition to the gritty feel of some biles due to excessive crystalline precipitation), and it is this that occasionally when a spurt of gastric acid juice reached the duodenum, besides causing the aforesaid turbidity it creates an *effervescence* that is quite noticeable and continues for some time. It resembles closely the reaction seen in the urine containing carbonates on adding acetic acid, and suggests the possibility of detecting in the bile a carbonate (or phosphate) diathesis which may be concerned in calculi formation of the calcium variety. This point I believe will bear watching in the future. I have not encountered this turbidity of bile in cases in which there is gastric anacidity or achylia, nor so frequently, or with such a dense turbidity in those cases having gastric subacidity, and since it is in just this group of gastric curves that the chief diagnostic relationship to cholelithiasis lies, I would make the suggestion that in all cases the bile being studied should be artificially acidulated with hydrochloric acid and the resultant turbidity microscopically and chemically investigated.

I hope by now I have made clear the reason why I believe the general hypothesis upon which I have been working is sustainable and that you will now more fully appreciate the reasonableness of my arriving at certain conclusions in regard to whose tenability I solicit your critical weighing of the evidence I have put before you. It sums up into this, and brings me back to one of the early paragraphs of this communication, namely, that by this method of direct (hormonic ?) stimulation of the contrary innervation of the gall-bladder and the duct sphincter I believe it is possible to drain the biliary system, to actually empty the gall-bladder, partially or wholly of its *fluid* contents, and to segregate the several biles recovered (somewhat roughly I admit) in such a manner as to make it practically possible to make certain differential diagnostic inferences as to the state of health or disease of the several components of the biliary system in a scientifically correct manner not hitherto attainable. I shall have to ask you to refer to my four former papers<sup>5 6 7 8</sup> for a *résumé* of the possible diagnostic inferences, and later on I shall bring my diagnostic observations up to date.

Now if I have presented my argument sufficiently clearly, and if it can be temporarily admitted, and perhaps definitely proved in the future (and I shall have some suggestions to offer later as to how this direct proof can be obtained) that it is possible not only to drain the bile ducts and the liver of its secreting bile, but also the gall-bladder itself, then I need not now do more than to direct your attention to the possibilities that this method opens up for the treatment of various biliary states that heretofore have been best attained by purely surgical methods and to stimulate your enthusiasm for investigating into the precursory and probably functional states of biliary disorders of motor, secretory and nervous origin

which, if allowed to continue, will almost invariably lead to inflammatory, infective or calculus-forming states of disease.

In my opinion the most hopeful feature of this method lies in its practicability of investigating, by clinical experimental observations, in the attempt to detect some of the physiologic alterations of *function* of the gall-bladder, liver and ducts; disorders of function, such as the hitherto undescribed entity of functional atony of the gall-bladder; spasm of the ducts and lowered velocity rates of liver secretion, which directly contribute to slowing up the excretion of bile and bring about biliary stasis.

For it is biliary stasis that all writers are in agreement as being the forerunner of gall-stones and of inflamed and infected gall-bladders and gall ducts. Any successful method of directly determining biliary stasis immediately opens up fields of investigating and explaining such common conditions as we loosely call biliousness, liver lethargy, hepatic torpor, with their resultant migraine and migrainoid attacks with biliary vomiting. Permit me to quote from another article<sup>10</sup> I have recently written: "If we are to attack the great problem of gall-bladder disease, gall-stones and gall-bladder and duct catarrhs and infections, and attack it at its source, we must give this lightly passed over symptom-grouping called "biliousness" our serious attention. Thus far our attitude toward the gall-bladder problem has been one of *correction* of the full-blown stages of formed calculi and active catarrhal infection, and the means adopted have been largely surgical. The surgeon's achievements in pioneering this subject have been very great. Their results have been at times brilliant, often less satisfactory and not infrequently bad, requiring many and repeated surgical maneuvers usually eventuating in that *bête noir* of surgery, distorting post-operative or postinflammatory adhesions, so that the state of chronic invalidism of the patient is a heavy cross to bear. What we must do is to attack the problem with methods of *prevention* of gall-bladder disease, with its sequelæ, and this brings us back to attacking the biliary stasis which is at the root of the matter. Biliary stasis is followed by overdistention of gall-bladder and ducts, leading perhaps to what we may designate in the future as gall-bladder atony. This engenders catarrhal states of gall-bladder and duct mucosa, weakening resistance and permits of successful implantation of infecting microorganisms, filtered out from the portal blood or carried directly to the gall-bladder by the systemic blood or by the lymphatics, or ascending to the gall-bladder by way of the duodenum and the common duct or passing through the serosa of the gall-bladder from direct contact with contaminated peritoneal coverings of neighborhood viscera. Biliary stasis, with its concentrated bile and precipitation of its crystalline chemistry, plus catarrh, plus infection, means gall-stones. Therefore it is

<sup>10</sup> Lyon, B. B. Vincent: Some Aspects of the Diagnosis and Treatment of Cholecystitis and Cholelithiasis, Medical Clinics of North America, March, 1920.

biliary *stasis* that we must attack if we are to prevent gall-stones, catarrhs or infections."

Can we do so? I think we may entertain greater hopes of so doing if wide application can be made of this method of investigating into some of the predisposing factors and conditions that we know enter into the precalculous and preinfective states of the gall-bladder and ducts. I would suggest that the problem be attacked first by a careful clinical study of that large group of individuals who have periodic or cyclic attacks of so-called "biliousness," or "lazy" liver, ushered in by gradual loss of ambition, increasing sense of mental and physical heaviness or lethargy, constipation, furring of tongue, metallic sense of taste, loss of appetite and headaches and eye-aches of greater or less severity; many attacks terminating in the true migraine type, accompanied by nausea and vomiting, various ocular manifestations, dizziness and various degrees of prostration, a group of symptoms that in some degree we meet within our practice nearly every day. These patients usually find out for themselves that their complaint is best relieved by calomel or other of the so-called cholagogic group of medicines, and they learn, furthermore, that they are rarely cured by such means. Various pharmaceutical houses, to say nothing of many independent pseudo-doctors, have made fortunes, as well as paid for a lot of expensive advertising and literary propaganda, from exploiting this very common symptom-complex, advising this or that laxative pill or liquid medicine, which at best gives only a modicum of temporary relief.

I surmise that it will surprise many of you to recover from such patients four ounces of more static bile from a gall-bladder whose normal capacity all anatomists agree in limiting from  $1\frac{1}{2}$  to  $2\frac{1}{2}$  ounces. When such amounts are recoverable I think it reasonable to assume that such a gall-bladder is being stretched beyond its physiologic limits of distensibility, and if this stretching is continued such a gall-bladder loses its normal tonicity of contraction and the organ becomes functionally atonic (as does any other hollow and distensible viscus, such as the stomach, the colon, the bladder, etc.) and is physiologically incapable of emptying its contents completely. In the future we may be able to speak of such gall-bladders in terms of "residual bile," as we now are quite accustomed to the term of residual urine in the domain of the urologists. I hazard the prediction that in the future the duodenal tube may be used quite as easily and freely, and certainly far more painlessly, to empty such distended gall-bladders as the urinary catheter is used today. And no thinking doctor of today would dare challenge the statement that such functional(?) disorders of the gall-bladder do not have a most important bearing on the production of later and more serious gall-bladder diseases.

I see no great difficulties in studying by this direct means the clinical-pharmaceutical action of the whole series of so-called chola-

gogues (and such a study is already under way) by both directly douching the duodenum with these drugs in solution and by allowing them to be swallowed and passed through (or absorbed by) the stomach and note the rate and amount and type of biliary discharge. The same method of study can be paralleled in investigating the recent pharmaceutical preparations designated as hormones to stimulate pancreatic secretion and the recovered mixed bile and pancreatic juice can be studied for pancreatic efficiency. Similarly the group of antispasmodics, atropin, belladonna, benzyl-benzoate can be investigated, as well as the effect of Witte's peptone or of egg albumen subjected to preliminary artificial gastric digestion, and of various meat extracts and extractives.

There are unbounded avenues of investigation waiting to be taken up, all of which will have a direct or indirect bearing on solving the great problem of gall-bladder disease, namely, the prevention of biliary stasis and thereby that of cholelithiasis.

One very practical field of usefulness came to my attention at the Methodist Hospital during my summer service. Several fully convalescent typhoid patients were retained in the hospital because their cultures from either urine or stool still came back "positive for typhoid bacilli," and they could, therefore, not be discharged on account of the danger of becoming "carriers." Several such patients were found to be harboring typhoid bacilli in their static gall-bladder bile. This is the time to treat such a case by non-surgical drainage, and that patient may not need to be operated upon several years, or even decades later for the removal of gall-stones from whose nuclei the pathologist may report the bacteriological recovery of a pure culture of the *Bacillus typhosus*, as has happened quite frequently in the past. I would suggest considering the advisability of testing directly the biliary excretions of all convalescent typhoid patients, both to prevent their becoming "carriers" and to guard them from later developing more serious gall-bladder disease.

One good reaction, as the pendulum swings from one extreme to the other. I am sure many of us have welcomed as being a rational one, and that is to stop starving our typhoid cases as we used to do ten to fifteen years ago and to start feeding them on a sensible dietetic plan as advocated several years ago by Coleman. Since this plan of feeding has been more widely carried out we have seen fewer instances of a complicating typhoid cholecystitis, for the simple reason that we are now giving the patient food mixtures that produce an acid chyme capable of changing proteids into proteoses and peptones and thus deliver to the duodenum a food hormone that permits the duct sphincter to relax and the gall-bladder to express its static bile. I think this point is worth considering also in connection with the dietetic management, assisted by artificial gastric juice, in those subacute and chronic infections of long standing that tend to create a state of gastric subacidity.

For similar reasons in treating my selected medical group of duodenal ulcer cases (the non-obstructive type, etc.) by duodenal feeding I am draining their gall-bladder once a week to prevent the bile from becoming static during that three or four weeks period in which the duodenum is deprived of the food-bearing acid gastric chyme which acts as one of the physiologic reflex agencies for bile discharge.

This is the best place to refer to the natural limitations of this method and to the fortunately small group of diseased states of the gall-bladder and ducts in which it is probably impossible to empty the gall-bladder. I refer especially to those cases in which the cystic duct is obstructed, although this may prove to depend somewhat on the nature of the obstruction and upon the relative tonicity remaining to the gall-bladder. I do not believe it will be possible to empty the gall-bladder when a calculus is embedded in the swollen and congested lumen of the cystic duct, although Nature has, in times past, accomplished this even when unassisted. It will be impossible, naturally to empty the gall-bladder when this duct is mechanically obstructed by inflammatory adhesions or when an enlarged lymphatic gland alongside of the cysticus obstructs it by direct mechanical pressure, as Deaver<sup>11</sup> called our attention to some years ago. Nor do states of hydrops, due to swelling of the mucous glands at the neck of the gall-bladder, offer much better chance of success, and certainly not when a mass of calculi make a stony cast filling the entire lumen of the gall-bladder sac.

The practical value of this method, so far as it concerns treatment, is that it adds greatly to our medical armamentarium in treating all of the recognizable early states of biliary stasis, many of the later states of biliary stasis as seen in patients with atrophic gastritis (often preceded by oral sepsis), with pernicious anemia, with certain forms of auto-intoxication and that large group presenting symptoms of both early and late migraine states. I have already reported my results in treating simple catarrhal jaundice in which I was able to reduce the duration of the disease by 52 per cent. in one group of patients as compared to a second group treated by the customary symptomatic or expectant plan, and I have learned, through personal communications, that other doctors have since had even greater success with the method.

I believe that by this method we can adopt in a non-surgical way the generally accepted surgical principles of free drainage as applied to some of the early catarrhal and infective conditions of the biliary tract, and I believe do it thoroughly and effectively, with a far better check on how effective it really is and with an avoidance of certain definite surgical risks. It cannot and need not supersede surgery—the very necessary surgery—for the removal of calculi, for the drainage of acute or chronic empyema, for the removal of

<sup>11</sup> International Clinics, vol. i, eighteenth series.  
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the gall-bladder in gangrenous cholecystitis or when its wall or lymphatic glands are the seat of a chronic focus of infection, or of carcinoma, or for the relief of mechanical obstructions produced by adhesions, although it might be well used to *supplement* some of these operations and to further ultimate recovery of the patient. The physiologic mechanics of this method should appeal to the surgeon, and therefore what I had said in this paper need not offend the minds of those who think only from the surgical-mechanical angle that nothing is good or worth while doing unless it is done by means of the aseptic scalpel, and who continue to teach suffering humanity that the only royal road to health is by the "cut well, sew well, get well" route. I am not so sure that by the dead pathology of the autopsy room or by the living pathology as seen at the operating table we have obtained the complete picture of many diseases; we have caught the full-face view, but I feel convinced that we have missed many of the profiles, to say nothing of the full-length multiple-mirrored reflection. During the past two or three decades we have learned much of the later life history of disease. The development and extensive use of the microscope applied to examining in closer detail our autopsy material has taught us many facts of dead pathology. The wonderful accomplishments of surgeons during this time by their marvelous dissection and removal of diseased tissues have taught us much of the living pathology of those earlier stages, that if uncorrected speed on the lethal end. It is true that we have been taught the characteristic lesions that diseases, if left unchecked, can by their very nature produce; but let us take a bird's-eye view of what has been accomplished in the past decade by that relatively small but brave band of physiologists who have come on with the giant stride of the seven league boots, and I opine that the wise doctor of the future will be he who with open mind can grasp the accepted facts of experimental physiology and by practical use of physiologic principles assist Nature to help herself. Not that we have not done much to correct by our increased knowledge and skill pathologic lesions, but that we should do still more to prevent them.

I confess, too, to have lost my enthusiasm for and my belief in the infallible diagnostic acumen of the intuitive genius who by simple touch of the "educated" finger can say that this patient has a chronic cholecystitis and that one a chronic appendicitis, and thereupon proceeds to remove the perhaps unoffending organ on the ground that its physiologic function is aborted or that it harbors a pathogenetic factor that menaces future health and leaves instead the too-often postoperative adhesion or the incisional hernia. Heaven knows that my dispensary clinic is only too full of the results of such faulty diagnosis and injudicious surgery.

And I find it difficult to believe that the trained master of living pathology can always tell by practised eye and touch that this gall-bladder, with its somewhat thickened and shrunken wall, is physio-

logically incompetent and incapable of resuming its function and make a bull's eye every time. A critical review of Case No. II will serve to support this contention.

You will see, then, that I am presenting this method of physiologically draining the gall-bladder (1) as a *means of diagnosis* of biliary diseases to supplement the usual clinical methods of diagnosis and the great help given us in many cases by the roentgenologist; (2) as an *alternative method of treatment* of many types of gall-bladder and duct disease in which there arises a question of opinion as to whether surgery is or is not emphatically and immediately indicated, and (3) as a *supplementary method* of postoperatively continuing the surgical principles of drainage in those cases incompletely cured by surgical measures alone.

To present the merits of this method of diagnosis and treatment it is clearly necessary that I submit for your inspection a few case reports of patients so treated, and to this end I ask your indulgence for a few minutes longer. These case reports have been selected for the purpose of illustrating different points contained in the subject-matter of my paper. I have many others that would serve equally as well.

The first case I am presenting was the very first patient of my series and illustrates what can be accomplished by this method postoperatively in treating acute cholelithiasis.

CASE I.—Miss A. I., aged seventeen years, was suffering with an infection of the common bile duct, with inflammatory swelling causing an obstruction of the duct. It had been essentially a chronic condition for two years, with intermittent acute exacerbations. This patient had had three major gall-bladder operations and two minor operations performed upon her in three years. The first one at the age of twelve years. In addition to this she had had six other admissions to the same hospital on both the surgical and medical services for non-operative measures for postsurgical sequelæ and had been treated by bed-rest, external applications, urotropin, the salicylates, morphin, codeine, sodium phosphate, nux vomica, cascara, calomel and other drugs, and was given various modifications of her diet, with at best only palliative effect.

At the end of this time she still had an infective cholelithiasis which was subject to acute remittent exacerbations of the most characteristic type. During the early spring of 1917, while in an acute attack, the surgeons in charge transferred her to me.

At that time she was definitely septic (of the chronic type), undernourished and intensely jaundiced. She had a leukocytosis of 17,000 to 26,000 with low polynuclear resistance. She was suffering intensely with acute paroxysmal upper abdominal pain and persistent nausea and vomiting. The muscles of her upper right quadrant were rigid and exquisitely sensitive to both light and deep palpation. In short, she presented the picture of a case that would be considered clearly surgical were it not for the fact

that she already had had her gall-bladder drained for an acute empyema. Six months later her gall-bladder was removed and her common duct drained. One year subsequently the common duct was again drained and several small stones were removed from the common duct, stones which had probably formed in the duct as a result of biliary stasis, associated with the persistent common duct infection and obstruction. The surgeons had still vivid recollections of the difficulties encountered in the last two operations of exposing the operative field on account of the dense mass of inflammatory adhesions.

This, then, was the first patient upon whom this direct non-surgical method of drainage was attempted. I am citing this case in some detail to direct attention (1) to the fact that it was certainly not the type of case in which one would expect much success from a new and untried method of treatment and (2) that it resulted in a most successful outcome.

This patient's obstructed common duct was unplugged by the local douching of the duodenum by magnesium sulphate and by the use of hot bland inflammation-allaying solutions of boracic acid and Ringer's salt. In this case I believe the unplugging of the duct was more directly due to the effect of the latter two solutions, but I used the magnesium sulphate because I had just read Meltzer's article. On relieving the duct obstruction I recovered infected pathologic bile containing pus cells, inflammatory debris, crystalline pigments and bacteria. The *B. pyocyaneus* was isolated in pure culture from this bile. Incidentally it is of interest to note that this same organism was recovered from bile discharged from the abdominal sinus following her first operation five years earlier, and had doubtless persisted as the infecting agent, notwithstanding a thorough course of autogenous vaccination.

After the common bile duct had been unplugged it was kept open by continual duodenal-tube drainage for several days, with direct disinfection and cleansing of the duodenal zone with potassium permanganate and normal salt solution three or four times a day and duodenal feedings every fourth hour. After one week of this, biliary drainage for two hours, followed by duodenal disinfection, was practised every second day. By the third day following the inauguration of this direct method of treatment the critical picture of this patient had very materially improved; the paroxysmal pain subsided with the establishment of biliary drainage, the septic temperature dropped, the muscle rigidity relaxed, the intense jaundice lessened, the leukocytosis, which rose during the first three days from 17,000 to 26,000, gradually dropped. During the next four weeks there were several mild but never severe exacerbations, and from then onward her recovery was uninterrupted. By the ninth week the cultures from the bile which had continued to show the *B. pyocyaneus* were for the first time reported free from this organism. During this stage of her treatment and later she

was given a second long course of vaccination, which was carried on for two and a half months up to dosages of 3,000,000,000. During the next eighteen months she had two slight exacerbations, and on my return from France she reported herself at my clinic and was quite a changed girl; she had gained fifteen pounds in weight and had for the first time in my observation some natural color in her cheeks and a continued absence of jaundice. Besides, her acne, which was the worst I have ever seen, was very much improved. During this past year (1919) I have drained her common duct and irrigated her duodenum thirty-one times, partly because I have been using her case for some experimental work and partly because she has a fearful horror of a relapse, and because she states that she feels better after such treatments.

Her bile has been cultured several times this year and has been reported free from *B. pyocyaneus*. But to bring her case absolutely up to date for this paper I had her bile cultured three weeks ago and to my intense disappointment it was reported to contain *B. pyocyaneus*. I had been congratulating myself on her apparent absolute cure. I am somewhat easier in mind, however, to find that the larger colony counts are coming from her liver bile, and I suspect that she has a low-grade chronic infection of the liver itself. Under these circumstances, perhaps an absolute cure is too much to ask of any method of treatment. I believe, however, that her general restoration to such good health is in itself a most encouraging fact. Of course, a third set of vaccines have been prepared and will be carried through. This failure with vaccines, too, does not shatter my belief in their usefulness, for I have had too much assistance from them in the past. I shall continue to drain and disinfect her bile in the hope that final complete cure can be accomplished or at least will serve to ward off acute duct exacerbations.

I am very glad that this young woman has consented to let me present her so that you may see that her present state of health is very satisfactory. Of course, we should remember that her future health may be menaced with biliary obstruction on account of the many adhesions, happily no longer acutely inflamed, which still serve to distort the radiographic outline of her duodenum, and it is for this reason, too, that I shall continue to treat her duodenum with Ringer's and other solutions. With this and in keeping her bile draining as freely as possible lie the best chances of final success.<sup>12</sup>

I append the complete chronology of her case, with dates and diagnoses copied from the original records:

C. 1848. Oct. 5, 1912, to Oct. 31, 1912: Empyema of gall-bladder. Drainage.

<sup>12</sup> At this date of publication this patient is apparently cured, is working hard in a department store every day, and following five months of further biliary drainage and vaccine therapy no longer shows the presence of the *B. pyocyaneus*.

C. 3291. Jan. 6, 1913, to Jan. 11, 1913: Removal of tonsils and adenoids.

D. 6353. May 13, 1914, to June 8, 1914: Cholecystectomy and choledochostomy.

E. 500. June 23, 1914, to July 16, 1914: Repair of sinus from gall-bladder.

E. 6395. Apr. 16, 1915, to Apr. 22, 1915: Hysteria and cholangitis.

E. 7308. June 30, 1915, to July 10, 1915: Cholelithiasis (duct) and choledochostomy.

F. 1454. Aug. 12, 1915, to Aug. 26, 1915: Perigastric adhesions.

F. 3208. Oct. 27, 1915, to Nov. 8, 1915: Abdominal adhesions.

F. 6778. Apr. 15, 1916, to Apr. 22, 1916: Abdominal adhesions.

G. 707. July 3, 1916, to July 15, 1916: Surgical neurasthenia.

G. 4879. Jan. 9, 1917, to Mar. 5, 1917: Chronic cholangitis.

Methodist Hospital, April 2, 1917, to June 20, 1917: Acute cholangitis and duodenitis.

Treatment continued since April 2, 1917, up to present writing by method outlined in this paper.

CASE II.—This case, an operative one of cholelithiasis and cholecystitis, accurately diagnosed by this method and confirmed by the roentgenologist, had a cholecystostomy performed and surgical drainage for eleven days. It was found six weeks later, by this method, that he still had an infective catarrhal cholecystitis in which the identical group of organisms as those originally isolated were still recoverable. He has since then been treated postoperatively by physiologic drainage, with encouraging success. This is the first motive for reporting this case, and the second is to show that the operator cannot by visible and tactile observation of living pathology always tell the amount of physiologic function still left to a shrunken and apparently functionless gall-bladder unless it is completely fibrous. Some will say it would have been better surgical judgment to have resected this gall-bladder, on the grounds that its walls are probably the real source of the remaining infection. Perhaps so, but in that event this case might fall within my group of cholecystectomized postoperative cases who still continue to show evidences, clinical and direct, of infection. At any event it will be an excellent case to try out the merits of the method I am suggesting. I think it is well to bear in mind that the surgical principle of drainage in any case of cholecystitis depends for success upon how *efficiently* bile drainage can be secured and upon how *long* it can be maintained, plus the contributing effects of bed-rest and modification of diet. Whether or not the infection is cured (in the true as well as in the surgical symptomatic sense) will depend directly upon three factors: first the virulence of the infection, second the resistance of the gall-bladder mucosa and wall (as well as those of the ducts) and its capacity to recover from the effects of the infection, measured in terms of the third factor, the efficiency and duration

of the surgical drainage. After the surgical drainage tubes have been removed and the cholecystotomy wound has closed by adhesions or otherwise, *if the given gall-bladder has not been entirely relieved of its infection it is then left to Nature and to its own devices to do the rest.* The redevelopment of symptoms then becomes the apparent criterion of cure. It is here that the practical utility of this method for supplementary postoperative treatment becomes clearly apparent.

*Protocol of Case II.* Mr. J. H., a very robust man of forty-seven years, contracted influenza of the pandemic type, with bronchitis, in October, 1918. This was the only genuine infection of his entire life, although for twenty-five years he had suffered from chronic remittent attacks of migraine, which I believe may have been due to some degree of biliary stasis. His convalescence from the effects of the influenza was slow, and four months later he developed the first of five attacks of acute epigastric pain, colicky and cramp-like, followed by a dull aching and soreness, accompanied by vomiting, and during the last two attacks by jaundice of the mildest type. His stools were offensive and "gassy." During the four months' period of these attacks he had lost thirty-one pounds in weight. In none of the attacks was the pain ever referred to the back or to either shoulder, nor indeed even to the right hypochondrium.

Physical examination of his abdomen revealed *nothing* suggestive of gall-bladder, ulcer or appendix disease:

Examination of his stomach and duodenum revealed an infective type of anacid gastritis and duodenitis, and direct examination of his biliary system showed a pathologic "A" and "B" bile, the latter containing the greater abundance of mucopurulent elements, a swarming mixed bacterial flora and such an abundance of bile crystals as to impart a distinctly "gritty" feel to his bile. Cultures from "A" and "B" bile recovered the following organisms: *B. coli*, *pneumococcus capsulatus*, *Streptococcus viridans* and *Micrococcus tetragenus*. The recovery of three of this group of organisms strongly suggests the relationship of his gall-bladder infection to the preceding influenza with bronchitis.

A diagnosis of infective cholecystitis and choledochitis was made, with a suggested possibility of cholelithiasis, the latter being confirmed by the radiographic study of Dr. W. F. Manges. On account of the calculus state he was referred for operation. Sequence of events in his case:

*Operation*, October 16, 1919 (Dr. J. D. Elliott). Stomach and duodenum explored and declared surgically negative. No adhesions. Gall-bladder exposed and found shrunken and contracted, with thickened wall but no adhesions, and apparently it did not contain stones. However, on opening the gall-bladder it was found filled with a thickened greenish-black bile, similar to that of "B" bile, and between fifty and sixty small stones were scooped out, ranging between the smallest granules to large match-head size. The gall-

bladder was not removed (probably wisely) and rubber-tube drainage was sewed in with chromic gut. Surgical drainage was carried out for a total of eleven days. Postoperative recovery was uneventful.

Now, aside from the surgical removal of his gall-stones, was this man cured of his gall-bladder infection?

November 27, 1919. Mr. J. H. returned to me for reëxamination. Direct examination of his biliary system revealed "A" and "B" biles to be definitely pathologic, the latter containing a swarming bacterial flora, very many mucopurulent flakes which ran over 100 pus cells to the field, inflammatory debris, but a less evident deposition of bile crystals. Cultures from that bile recovered the identical group of four organisms as isolated before operation. Clearly then this patient had not been cured of his cholecystitis by the eleven days of surgical drainage.

Since November 27, 1919, he has had his biliary system physiologically drained by this method once a week, with gastric and duodenal disinfection, followed by transduodenal lavage with Ringer's salt or Jutte's solution, with steady improvement in the cytological findings. the mucopurulent shreds particularly have gradually decreased and the bacterial flora is less evident. He is being given, too, injections of an autogenous vaccine and is taking hydrochloric acid and pepsin and following an appropriate diet. This plan of treatment will be followed until ultimate cure is secured by the direct evidence shown in the cytology and bacteriology of his bile.

You will be interested to learn that this man's apparently shrunken and thickened gall-bladder wall is still capable of delivering bile under physiologic stimulation in amounts varying from two to four ounces. Certainly, the function of this man's gall-bladder was *not destroyed and gives promise of eventual restoration.*

To look at this gentleman as he sits before you, entirely symptom-free, with his good color and having regained his weight, no one would dream that he still had lurking in his gall-bladder a dangerous microbic infection capable of lighting up and producing further mischief unless carefully watched and controlled by this very simple and practical method.<sup>13</sup>

CASE III.—This case is reported because it illustrates what is possible of accomplishment in the treatment of biliary stasis, with low-grade infection of the gall-bladder and ducts, resulting in the severest type of migraine and evidence of early toxic arthritis. This may be called a "masked" gall-bladder disease, at no time giving rise to symptoms severe enough to warrant surgical consultation. Perhaps persistence in this method of treatment may result in true

<sup>13</sup> Since February, 1920, this patient has been treated at gradually lengthening intervals, and for the past three months has had a biliary drainage only once a month. Vaccine therapy has been continued. When last seen, on September 18, his biliary examination was quite normal. He has remained perfectly well and, in his own words, "never felt better in my life."

cures in many of these cases, especially if caught early. Certainly the relief of symptoms after so many other measures have been unsuccessfully tried, entitles us to place high hopes on this method of physiologic biliary drainage combined with transduodenal lavage and the use of specially selected contributing measures to meet various angles of disorders and diseases, only brought to light by a searching diagnostic review of the various systems of the body. This case is also worthy of report to illustrate how the primary focus of infection may give rise to successive foci in the gastro-intestinal tract even though the primary focus itself has become quiescent or has disappeared; it also illustrates the advance of gastro-intestinal disease from one zone to another, with a corresponding transition in symptoms. Finally, this case illustrates the ease with which this method may be carried out, after a little preliminary instruction even in the hands of relatively unskilled doctors or attendants.

Mrs. "K." was referred to me on August 27, 1919, by Dr. F. O. Lewis. She was forty-nine years old and married, with one daughter aged sixteen years, her only conception.

Her chief complaints were many, but in the order of importance to the patient were:

1. Headaches of great severity and frequent occurrence in cycles of variable duration.
2. Gas on the stomach, with nocturnal and diurnal cardiac palpitation.
3. Dizziness and light-headedness and easy fatigue.
4. General abdominal bloating, with wandering pinching and cutting, general abdominal pains, with sensations of "raw spots" in the abdomen.
5. Intestinal gas of offensive odor.
6. Obstinate constipation, if not daily prevented by laxatives, resulting in increasing laxative habit for fifteen years. Stools contain much mucus in the form of coarse shreds, casts and ropes, and stools are described to conform to type of spastic constipation.
7. Progressive loss of weight and strength.

*Past Medical History:* Measles, parotitis and pertussis in childhood, and since then has never been sick in bed except with "sick headaches," which have occurred with increasing severity and frequency.

*Present Illness:* She states that she has had "bilious headaches" ever since she can remember, many of them accompanied by sick stomach and occasional vomiting. For twenty-five years her headaches were associated with nausea and sour, gassy stomach, but about ten years ago the gastric symptoms disappeared and were replaced by lower abdominal bloating, cutting and pinching abdominal pains and increasing mucus in the stools, with increasing constipation punctuated by intermittent diarrheal periods. The headaches increased in severity, frequency and duration, and are described as follows: They begin as left orbital and pass to the



left temporal region—less frequently beginning in the right orbital region. They are very severe, usually putting her to bed; formerly lasting for eight to ten hours, for several months past they have lasted for two to four days. After the acute headache has stopped she will try to eat a little, and about two to four hours later gets a diffuse headache, with especially a sense of intense pressure on top of the head. She finds it is always worse after the head is exposed to cold or drafts, and so wraps her head in a hot woolen cloth, with some relief. Recently she has noticed that the bilious, sour stomach is not so noticeable a prodromal symptom, and has been replaced by pain in the arch of the left foot and under the toes, which become stiff and swollen and burn. The following day she wakes up with a sick headache. She says if she were not very careful with her diet she would have headache all the time; that she has not eaten any fried foods in nine years, because these always aggravate the headaches. She eats boiled meat (beef, lamb, chicken) with agreement, but thinks vegetables cause bloating and intestinal gas and increase the headaches. Tea and sweets also disagree. She states that for twelve to fifteen years she has been troubled with her teeth, with cavities and advancing pyorrhea, and that three months ago all of her teeth were extracted. She fights constipation all the time, because her headaches have been less when her bowels move freely, and she has occasional spells of diarrhea, with much mucus. She uses daily three to eight "pink laxative" pills and Pluto water. Her skin became sallow several years ago, but has become progressively browner and more bronzed. She has noticed progressive loss of strength and weight during the past eleven years, the later totaling 19 pounds, from 110 to 91. She has also noticed increasing depression and melancholia, and has been told that her case was "incurable." She has worn eye glasses for two years without any improvement in the headaches.

*On Physical Examination:* She presented the typical appearance of one suffering from a chronic intoxication or infection. Asthenic type. Thin, anemic, tired-looking, with dark circles under eyes and sallow brown complexion, with dry skin and thin, gray, dry, lusterless hair. Eyes: negative except for dilated pupils.

Nose, tonsils and glands are negative.

Tongue coated; gums clean and well healed and wears well-fitting double plates.

Dermatographia well marked. No typical Addisonian findings.

Thorax long and emaciated.

Lungs: Fibroid apices.

Heart: Normal in S. and P., no M. Tone fair, rate 80 to 90.

Pulses equal. Blood-pressure 140-90. Very little sclerotic change in radials, brachials or temporals.

Abdomen: That of the visceroptotic—space encroached upon by long thorax, flat epigastrium and bulging umbilical and iliac zones—with visible peristalsis.

Costal angle medium narrow. Visceroptotic index, 0.83.

Abdominal aorta and right iliac artery uncovered, forcibly pulsating and tender. Tender also over solar plexus and over sigmoid, the latter being distinctly spastic and contracted.

Stomach in normal position but dilated.

Transverse colon ptotic. Right kidney floating.

Rectal examination reveals only internal hemorrhoids and external tags.

Spinal Examination: Slight scoliosis to left and soreness over the left transverse processes of the fourth to eighth dorsal vertebrae, and pain on pressure over the left transverse process of the eleventh dorsal vertebra.

Extremities and joints negative.

Deep reflexes normal.

*Special and Technical Examinations:* Urinalyses show only faint traces of albumin, intermittent presence of indican and hyalin casts. No fixation of specific gravity; tendency to polyuria. No retention of chlorides or urea nitrogen.

Functional phenolsulphonephthalein test: 1st hour, 370 mils., 50 per cent. elimination; 2d hour, 160 mils., 20 per cent. elimination; 3d hour, 120 mils., trace; total, 650 mils., 70 per cent. plus elimination.

Blood. Moderate secondary anemia. White blood cells, 6300. Wassermann negative.

*Gastro-intestinal examination:* Summary of fractional gastric study:

Fasting stomach: No food rests; much mucus; 5 mils. F.Hcl = 0; Total acid = 20. Blood, 0.

Microorganisms plus, including *Leptothrix buccalis*. Few polys.

Fractional curve of anacidity, hypermotility and biliary regurgitation.

Mucus greatly increased. Enzymes and proenzymes present but deficient.

Wolff-Junghan's test for soluble albumin 1 to 40. Increased intestinal motility. Five grains of carmine powder given in a mixed meal appeared in stool in ten hours and was completely defecated at fifteen hours.

*Duodenobiliary examination:*

After mouth and stomach cleansing and disinfection, duodenal tube entered duodenal biliary zone in sixteen minutes. Much duodenal mucus; sphincter of bile duct open and bile discharging. Flow accelerated by douching with magnesium sulphate.

"A" bile diluted by small amount of magnesium sulphate. 36 mils., light yellow, clear, syrupy.

"B" bile 51 mils. dark greenish-black, molasses-like static bile with few mucopurulent floccules containing bile-stained columnar epithelium and leukocytes. Bacteria very evident.

Cultures from "B" bile: *B. pyocyaneus* and *Staphylococcus aureus*.

"C" bile light lemon yellow, thinly mucoid.

*Examination of bile for pancreatic activity:*

Trypsin: 1 mil. of bile digests 10 mils. of 0.1 per cent. solution of casein in fifteen minutes.

Amylopsin: 1 mil of bile digests 5 mils. of 1 per cent. solution of starch in thirty minutes.

*Stool Examinations:* Spastic scybalous and small calibered sausage masses pointed at one end, superficially covered with shaggy, stringy mucus, rather pale yellow color. No gross indigestion of food. Occult blood positive.

*Microscopically:* A few muscle fibers, with preserved connective tissue, but partially digested. No starch remnants. No neutral fat but many fatty acid crystals (split fats); slightly increased cellulose.

Bacterial smears chiefly Gram-negative.

*Diagnostic Deductions:* In somewhat their order of importance:

*General Diagnosis:*

A. Major.

1. Chronic toxemia.

(a) Bacterial, with first focus of infection probably in teeth and gums (oral sepsis, now clean) passed to secondary foci in stomach, gall-bladder and colon.

(b) Metabolic, from static biliary source; from intestinal and renal sources and from static vascular (splanchnic) circulation due to visceroptosis.

2. Visceroptosis.

3. Chronic cholecystitis (masked), of low grade of infective virulency and preceded by chronic biliary stasis.

4. Chronic mucous colitis, with spastic constipation, probably first due to vagotonia and now continued, owing to erosive areas in colon.

B. Minor.

1. Chronic interstitial nephritis—probably early and secondary.

2. Fibroid lungs—probably quiescent or healed tuberculosis.

3. Sympatheticotonia (dilated pupils, relatively high pressure, subsecretory states—dermatographia).

4. Low grade early toxic arthritis.

5. Chronic atrophic gastritis.

*Conduct of treatment decided upon:*

I. *General.* To improve toxemia by appropriate treatment of the

(a) Visceroptosis (bed-rest, elevation of foot of bed, properly selected and arranged diet to improve assimilation and weight-building, proper abdominal support).

(b) Mucous colitis (breaking chronic laxative habit and substituting "senna-fruit paste," which is gradually withdrawn; proper dietary; associated effect of transduodenal lavage and other topical treatment).

II. Direct treatment by physiological-biliary drainage to arrest the progress of the cholecystitis and to attack the biliary stasis,

considered to be the dominant causative factor of the migraine attacks (her most bitter chief complaint).

*Method of Direct Treatment.* Biweekly physiological biliary drainage, preceded by mouth disinfection, gastric lavage and disinfection, with potassium permanganate or silver nitrate.

After physiological biliary drainage and disinfection of duodenobiliary zone a transduodenal lavage is given of Ringer's salt, with 1 per cent. sodium sulphate, in amounts of 250 to 350 mls. Given very slowly by drip method.

This treatment was carried out for three or four weeks at the Methodist Hospital for the purpose of training the patient and nurse and to teach the principles of a visceroptotic rest cure.

Treatment then continued by nurse at patient's home in Easton, Pa., being given biweekly for five weeks more, then once a week.

Visceroptotic rest cure treatment continued.

High caloric diet, suited to her achylia, and digestion aided by substitution gastric digestants. Benzyl-benzoate was used for its effect on the spastic colitis. No laxative was given except a 2 per cent. senna paste, later decreased to 0.5 per cent.

The dark green-black static bile of molasses consistency was evident in each of the first three or four treatments in amounts of 75 to 120 mls., but thereafter gradually lightened in color to a golden yellow, the inflammatory cytological elements lessened and the bacterial content decreased and all biles showed improvement in gross appearance. An autogenous vaccine of *B. pyocyaneus* and *Staphylococcus aureus* was prepared and given twice weekly.

*Progress of Case.* Notes of December 17, 1919. Patient shows a wonderful improvement. Looks so much better; color less sallow—brown; skin less parchment-like; dark circles under eyes are practically gone. She has much more endurance, energy and strength. She has gained 15 pounds in three and a half months, from 91 to 106½ pounds (kimona weight). Her bowels are moving once or twice daily, with one-half teaspoonful of 0.5 per cent. senna fruit paste at bedtime. The mucus has disappeared nearly completely from the stools. The wandering abdominal pains are no longer felt and the spastic type of bowel movement is no longer seen.

Best of all, from her standpoint, the headaches have from the onset of treatment been much less frequent, never severe, and for the past ten weeks she has had none.

How long her improvement will last or what will be the future development when treatment is finally interrupted I do not pretend to even guess.<sup>14</sup> I am not inclined to believe in so-called "cures"

<sup>14</sup> This patient returned to her home and continued self-treatment by this method three or four times a month. She was last examined in the office in July, 1920, and appeared to be remarkably improved. The appearance of the bile was nearly normal, the swarthinness of her complexion had disappeared and her endurance was much greater. She had maintained her gain of 15 pounds in weight, she had had no severe headaches and her bowels are moving twice daily, with no other laxative than senna fruit paste once a day.

of essentially chronic disease. Arrest of symptoms, quiescence of lesions, yes; but "cures" in the true sense I do not believe in.

I cannot close this communication without giving my hearty and sincere thanks to my associate worker, Dr. Henry J. Bartle, who has made many practical suggestions, and to Drs. Russell Richardson, S. W. Sappington, John A. Kolmer and H. B. Anderson, respectively pathologists to the Methodist, Hahnemann, Polyclinic and Pennsylvania Hospitals, for their painstaking bacteriologic work on specimens of bile submitted to them.

## GLUCOSE AS AN ADJUNCT MEASURE IN THE THERAPY OF PNEUMONIA.

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WHEN the epidemic of pneumonia which followed influenza in 1918-19 struck the army camps we were dealing with 98.2 per cent. of pneumonias at the U. S. Army Base Hospital, Fort Sam Houston, Texas, for which we had no specific therapy. In a series of 819 cases which developed during this season the available data on sputum examinations indicate that we had the small percentage of 1.8 per cent. of pneumococcus type I variety, for which alone anti-pneumococcic serum type I is available. These data are not complete, due to the fact that in the extreme rush it was impossible to get complete bacteriological reports on all cases; however, they bring forth a true picture of that which is available for reference. In my series of 137 cases reported the incidence of pneumococcus type I was 2.4 per cent., thus still having 97.6 per cent. of cases for which there was no specific therapy.

Such a problem as this naturally raises the question, What is best to do under the circumstances? There being no specific therapy, can we do something in a non-specific way, and what?

In this search for something, something which might help the human organism overwhelmed with infection, I began to use aqueous solution of glucose intravenously. Some other camps had begun to use it; there was a favorable impression as to its efficacy, which seemed justifiable for the procedure. There was practically no literature available on its use in pneumonia.

Naturally there were many questions that arose in my mind at that time, for it was like starting a new experiment in a laboratory, questions which I jotted down at that time in my note-book, for I was going to try to find explanations for these, and answer

questions which I can well bring out even now, for no doubt those very questions will arise in anyone's mind who makes an attempt to use glucose therapeutically with an intelligent conception as to its effects. The questions were these:

1. What concentration of glucose should be used?
2. Should it be made up with distilled water or with normal saline?
3. What intervals should be used for its administration?
4. What is the real indication for its use?
5. Is the elimination better in these cases as compared with those who do not get glucose?
6. Does it produce a fall of temperature?
7. Has it any specific effect on osmosis of the lung tissues due to its hypertonicity?
8. Is there any lysis of red blood corpuscles? Can this be demonstrated either by direct smears from blood, by separating the plasma or by the presence of hemoglobinuria?
9. What quantity of glucose should be used at each dose?
10. What are the chills which at times accompany the intravenous administration of glucose due to, and how can they be prevented?
11. What is the explanation of the slowing of the pulse-rate and the improvement of its volume?
12. Why is the patient more comfortable immediately following its intravenous administration?
13. Is there any rise or a fall of blood-pressure?
14. How rapidly can it be given and how slowly should it be given?
15. Does the administration of glucose change the clotting time of blood?
16. Does it stimulate leukocytosis?
17. How much of the glucose is used for bodily nutrition?
18. Why is it advantageous over normal saline?
19. Is extravasation of glucose into tissues at the point of administration alarming?

These then were some of the questions that arose in my mind at the beginning and during the time that I used glucose therapy. For many of these I was able to find an explanation, for others, due to lack of time and inaccessibility to substantial research, I was not. However, I shall take up each one of these questions and present my findings, my attempts toward solving them and give them to you as I solved them.

1 and 2. I found that different concentrations, ranging from 4 to 40 per cent., had been used. The answer then was rather a vague one, and to solve it I set up two series of tubes in the laboratory, one series of glucose, ranging from 1 to 20 per cent., made up in distilled water the other made up in normal saline. To these I added a suspension of human red blood corpuscles and placed them in the

incubator for one hour at  $37.5^{\circ}$  C., then on ice over-night, making the final reading in the morning. The result was as follows:

In the distilled water 1 to 5 per cent. hemolysis was present. In the distilled water 5 per cent. and above no hemolysis.

In the normal saline no hemolysis in any concentration. This proved one point to me: as long as I would keep above 5 per cent. solution I was safe so far as the question of hemolysis was concerned, and in the normal saline any concentration could be used.

I compromised on a 10 per cent. solution. 250 c.c. of this, for this was the quantity I used routinely, figured 100 calories, the solution being not thick but convenient for administration. In cases in which the disease was protracted where the question of nutrition came up I used 30 per cent. solution in an attempt to increase the carbohydrate intake to 300 calories per dose.

Erlanger and Woodyatt, in their experimental work, found that one can inject 0.8 to 0.9 gram per kg. body weight per hour for several hours without producing glucosuria. Thus for a man weighing 50 kg. one could inject 50 times 0.9 time 24 = 1080 grams or 1.08 kg. or over 2 pounds of sugar per day without producing glucosuria. In fact, Woodyatt cites a case in which he has been able to supply 6000 calories per day without producing glucosuria.

This point was a very interesting one to me, for it brought forth a proof that at a moderate administration there was no danger of the glucose passing through the renal filter, thus making one's work a blind issue.

3. In regard to the interval between the administrations I found that more than two doses per day were rarely necessary. In acute cases with high fever and prostration one administration in the morning, after the patient has had his bath and has been fixed up, and one after supper, when he is ready to retire for the night, were all that was found necessary. Following the administration the patient would always fall asleep and have a good rest; he would perspire, following which his temperature would drop 1 to  $3^{\circ}$ . The rest in itself was a great factor, for to a human machine that is whipped up above its normal capacity if you can give rest and sleep and slow the pulse, reduce the temperature, you have done as much as any conscientious physician can ever hope to do. You have saved the overhead expense which was threatening with bankruptcy. These were the five things which glucose always did for the patient:

1. It made him comfortable.
2. It produced sleep and rest.
3. It reduced the temperature.
4. It increased the elimination through kidneys and skin.
5. It slowed the heart and increased the pulse volume.

When only one dose a day was administered it was always given in the evening, for thus it invariably ensured the patient a good

night's rest, and in the morning one could see the bright countenance following a night's rest as compared with one who spent a sleepless night. His fighting chances thus undoubtedly were increased.

4. About the indication for glucose I would say any febrile condition is an indication for its use. When you have fever there you deal with a potential acidosis and a toxemia. This you can combat by the intravenous use of carbohydrates (glucose). You can reduce fever by its administration; you can make an uncomfortable patient comfortable; you help to tide him over. You can do no harm, only good.

5. As far as elimination is concerned, administration of glucose is followed by polyuria. The patient perspires profusely. Thus the two channels of elimination are both reached promptly and effectively.

6. Intravenous administration is followed by a drop of temperature of 1 to 3°. The increased perspiration with evaporation is what makes this drop in the temperature. Renal elimination may be an additional factor here as well.

7. In regard to its osmotic effect on the lung due to its hypertonicity I took up this question with Sollmann, of Western Reserve University. He says: "This is highly improbable. Experimental pulmonary edema is not prevented or influenced in the slightest degree by that factor. Atropin is also useless. The fluid is doubtless due to endothelial injury."

8. To determine whether or not there is any lysis in the blood stream I made the following experiments:

(a) I took blood at the beginning, during, at the end and eight hours after the administration of glucose from the same vein into which the needle was inserted (median basilic), some 20 cm. higher up toward the shoulder, making smears and placing the rest in small tubes on ice over-night. This experiment was not successful, as my controls showed lysis while the glucose specimens showed no lysis. Thus faulty technic was undoubtedly used, perhaps boiling of the syringes being at fault. The smears showed no changes of the corpuscles.

(b) Several series of urines were collected for one or more voidings before glucose administration, and on each subsequent voiding after the administration, each tested for occult blood, with the following results:

Name.	Specimen before glucose.	Specimen after glucose, successive voidings.	Fehling's test for sugar.
D. . . . .	—	— — — — —	—
S. . . . .	— —	— — — — —	—
C. . . . .	—	— — — — —	—
A. . . . .	—	— — — — —	—
Lu. . . . .	—	— — — — —	—
La. . . . .	—	— — — — —	—
— negative.			



This then would show there is no hemolysis, for if present the hemoglobin would have to be eliminated through the kidneys and give a positive test in the urine.

9. The quantity used can be considerable provided the administration is slow. Even a small quantity of 200 to 300 c.c. if given rapidly may show traces of glucose in the urine, but if given slowly there is practically no limit to the quantity which can be used, for, as mentioned, Woodyatt has been able to give 6000 calories in one day. This is such an overwhelming proof that one cannot question the small quantities of 250 c.c. used here.

I have used 250 c.c., as this quantity is convenient to prepare. One can thus use 8-ounce bottles and prepare a large quantity at one time and keep them on hand, for efficiency of this work depends on preparedness.

The total volume of circulating blood in the human body is approximately 2500 c.c. Injecting into the blood stream 250 c.c. of glucose solution one adds 10 per cent. to the total volume of the circulating fluid. Elimination through the kidneys and later perspiration quickly compensates for it.

10. Chills follow at times the intravenous administration of glucose the same as any intravenous medication, even that of normal saline. Just what they are due to I do not know. Literature does not offer us any definite explanation. They come and we have to deal with them without understanding their pathological physiology.

One can never predict when a chill will come. Frequently a patient will get three to five doses of glucose without any chills, then the next dose is accompanied by a chill, then again he may be free from them for a dose or two and again each subsequent dose followed by one. Or a patient may again start out with a chill following the first dose and not have any more. There has been no regularity whatever to these.

For a while I thought I had found a solution to this question by the use of morphin sulphate, 0.008 gm., and atropin sulphate, 0.00064 gm. When I began to use it for quite a long period I met with no chills. I thought I had made a discovery which could be utilized in chills due even to other causes. But my joy was of short duration, for I began to have them even after these opiate-atropin doses. However, they were not as frequent as formerly. Thus I believe that the morphin-atropin does prevent a certain number of them. Water used for the preparation of glucose solution and perhaps the glucose itself may have something to do with these chills. I used single distilled water.

These chills, however, are not serious. I have seen so many of them, perhaps 200 to 300, in the 1000 to 1200 administrations, and I failed to see any harm come from them. I always tell the patient that if they have a chill not to fear, as it is of no consequence. There is nothing special to do for these chills when they come, except to apply blankets and hot-water bottles to the body.

11. The slowing of the heart-beat and the increase in pulse volume is one of the most striking features of glucose administration. What is it due to? In the first place to the increased volume of the circulating fluids. In the second place to adding fuel to the heart muscle. In the third place through combating acidosis, thus reducing the stimulation of the vasomotor center and the sympathetics. I am sorry that I was not able to have a polygraph to graphically show this point.

12. In my routine administration of glucose I used 250 c.c. of a 10 per cent. solution, with morphin sulphate, 0.008 gm.; atropin sulphate, 0.00064 gm.; tincture digitalis, 1 c.c.

One can say: The rest and the feeling of comfort were due to the opiate. It was not. At the beginning I used no opiate and the same comfort and sleep followed. Opiate, you remember, was used in an attempt to combat the chills and also to add additional comfort and rest. It was the glucose mainly that produced the rest and the comfort.

It was also not the tincture of digitalis which produced the slowing of the heart-beat, for digitalis does not act so quickly. Besides the same slowing and improvement in the pulse volume happened at the beginning when I used no tincture digitalis. This I used to digitalize the heart muscle in case a further use of digitalis were indicated.

It was glucose itself that produced the rest, comfort and sleep through:

- (a) Additional volume of liquids to a febrile patient.
- (b) By combating the incipient acidosis.
- (c) By the increase of elimination.
- (d) By the decrease of temperature.
- (e) By strengthening the heart muscle directly and by the supply of carbohydrates to the tissues.

13. In regard to the rise or fall of blood-pressure the few careful readings I took showed a fall of 10 mm. Hg. immediately following its administration, the pressure coming up again to normal in forty-five to sixty minutes, as seen in the accompanying Chart I.

The removal of 5 c.c. of blood per kg. of body weight does not influence the blood-pressure (Macleod). From this I reason that if the removal of 5 c.c. of blood per kg. body weight does not influence the blood-pressure the addition of 5 c.c. of fluid per kg. body weight should also have no effect on blood-pressure. Thus, taking a man weighing 50 kg. and adding 5 c.c. of fluid, 50 times  $5 = 250$  c.c., which one ought to be able to add to the circulation without producing any effect. My blood-pressure readings seem to bring out this point.

14. As to the rapidity of administration. Naturally one cannot use too much speed for fear of cardiac dilatation. This applies especially to weakened hearts. I take fifteen to twenty-five minutes

for the administration of the 250 c.c. glucose. Too slow a procedure is also not advisable unless the receptacle can be kept at constant temperature, which is very impracticable at a bedside and quite unnecessary. All that is necessary is to allow for the cooling of the liquid before its entrance into the vein. I have made the following observations in order to show the amount of cooling during the procedure:

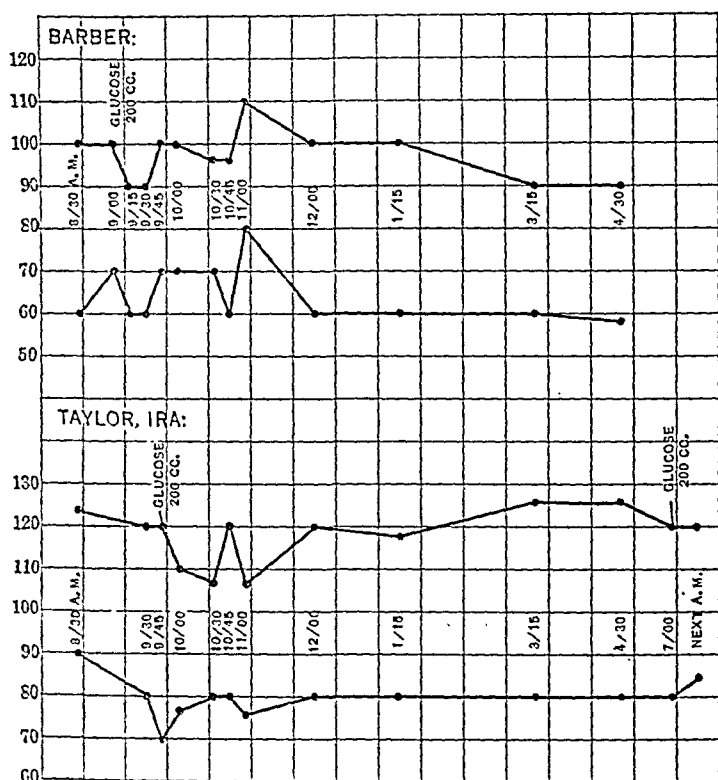


CHART I.—Observations on blood-pressure changes during intravenous administration of glucose.

A 250 c.c. bottle filled with glucose solution, a 3-way stopcock and a 10 c.c. syringe were used, the bottle being kept at a constant temperature. The exit temperature was measured from a No. 20 gauge needle in a test-tube.

Glucose, per cent.	Reservoir temperature.	Exit temperature.
10	37.5° C.	27° to 28°
10	78.0° C.	57° to 58°
30	37.5° C.	28° to 29°
30	68.0° C.	54° to 55°

From this one can see readily there is a considerable cooling of the liquid during the process of administration, so that the solution

should be considerably above the body temperature and not as usually is advocated and practised, at body temperature.

15 and 16. I have not made any determinations as to the clotting time of blood, neither that of the leukocytic stimulation.

17. All of the glucose is used for bodily nutrition. Repeated tests for sugar in the urine failed to show it in carefully collected specimens except once when a trace was found. When Woodyatt could administer 6000 calories without any production of glucosuria one naturally would not expect to find any from 100 to 300 calories.

18. In administration of normal saline one adds to the bodily fluids. This is true thus far. One does nothing more. With glucose you not only supply fluids, but you also supply food, fuel and that which you need for combating the incipient acidosis present. What does saline do to acidosis? It aggravates it (Macleod), and this is the point in question. With glucose you do all that a saline can do and a whole lot more.

19. Extravasation of glucose into the tissues is not alarming; it does no harm, the same as saline extravasation into the tissues.

I made an attempt in some cases to see what the concentration of glucose in the blood stream was just before and right after the administration of 250 c.c. of 10 per cent. glucose solution. The readings are as follows:

Name.	Date.	Before, per cent.	After, per cent.	Six hours later.
Mc.	November 27	0.130	0.190	
R.	November 28	0.146	0.269	
	November 29	0.11	0.22	0.104
P.	November 30	..	0.232	
M.	November 30	0.076	0.24	
	December 1	0.11	0.194	
S.	December 2	0.098	0.19	
W.	December 4	0.108	0.252	
P.	December 3	0.18	0.248	
P.	December 3	0.07	0.4	
	December 4	0.1	0.2	
M.	December 7	0.076	0.29	
R.	December 10	0.1	0.204	
	December 11	0.16	0.256	
	December 12	0.18	0.204	
	December 13	0.114	0.268	
B.	December 11	0.104	0.264	
	December 12	0.18	0.204	
T.	December 9	0.128	0.228	
Mc.	December 14	0.12	0.328	
	December 16	0.16	0.216	
A	December 5			
10.30 A.M.—Sugar before glucose, 0.160 per cent				
	10.50 A.M.— " after	"	0.232	"
	11.50 A.M.— " "	"	0.124	"
	12.50 P.M.— " "	"	0.152	"
	1.50 P.M.— " "	"	0.080	"
	2.50 P.M.— " "	"	0.080	"

To show the effect on pH before and after the administration of glucose the following determinations were made on blood:

Name.	Date.	pH before.	pH after.
R.	December 13	7.6	7.5
B.	December 12	7.1	7.1
Mc.	December 14	7.6	7.3
	December 16	7.4	7.4
W.	December 31	7.5	7.4
	January 1	7.4	7.2
G.	January 1	7.6	7.4
R.	January 10	7.5	7.3

The degree of acidosis is so slight that the variation naturally is small also. However, there is a definite decrease, as the figures show.

For the physiological action of glucose and its fate in the tissues I will cite Erlanger and Woodyatt:

When a single dose of glucose is injected there is a temporary increase of sugar in the circulation. The injected sugar passes rapidly out of the blood into the tissues. During its stay in the vessels the blood volume rises and a state of hydremic plethora develops, owing, doubtless, to the binding of water by the extra glucose in the vessels. This is shown by the fall of the hemoglobin percentage and a coincident fall in the blood-sugar percentage following the initial rise. These facts have been demonstrated by Brasol and confirmed and amplified by Biedl and Kraus. Similarly during the period of absorption following the alimentary administration of glucose there is at first a rise and later a return to normal of the blood-sugar percentage, and simultaneously with the latter a fall in the hemoglobin percentage.

You can inject 0.8 to 0.9 per kg. of body weight per hour for several hours without producing glucosuria. With the injection of 0.9 or more grams per kilogram per hour glucosuria develops and the rate of sugar excretion bears a definite relation to the rate of injection. During a sustained intravenous glucose injection at the sugar tolerance rate or below it glucose passes from the blood into the tissues and there undergoes chemical polymerization, oxidation, etc., at the same rate as that of injection. There is no material accumulation of glucose in the tissues. Injections at a subtolerant rate thus have a tendency to increase the glucose content in the blood without producing any appreciable increase in glucose in the tissues. The result is a disproportionate increase of the power of the blood to hold water and a state of hydremic plethora develops and presumably persists as long as the injections are sustained. The water held by the blood must come from the tissues or from the injection site or both. If the water injected with the glucose is not sufficient to satisfy the glucose in the blood some water will flow into the blood stream from the tissues. When

the glucose injection is stopped and the last of the injected glucose passes into the tissues the water previously held by the blood is suddenly discharged into the urine. This whole phenomenon differs essentially from that obtainable with inorganic salt solutions, because such salts when injected also pass into the tissues, but when once there are not destroyed. There is therefore a possibility of salt accumulation in the tissues holding water there and in part counteracting effects of the salt in the blood stream. With sustained intravenous injections of glucose at rates higher than 0.8 to 0.9 gm. per kg. per hour the glucose utilization fails to keep pace with that of the injection and the tendency is toward some accumulation of unchanged glucose. If the kidneys are functioning actively this glucose appears on the urinary side of the renal membrane and tends to collect water in this locality, probably for the same reason that glucose in the blood produces hydremia. This tendency is expressed as polyuria. Now if the diuresis exceeds water administration, water will flow from the tissues to the blood and thence to the urine, and hydremia will be sustained as long as the water supply is adequate. But if the kidneys do not function in this way most of the unchanged fraction of glucose injected remains in the body and tends to behave like a salt, causing accumulation of water in the tissues and body spaces wherever it may go. In shock cases the secretion of urine is likely to be impaired. Accordingly the most rational application of an intravenous glucose injection in shock would appear *a priori* on theoretical grounds to consist in long, sustained, uniform injections of subtolerant doses.

Author's Routine: 250 c.c. of a 10 per cent. aqueous solution of glucose are given b. i. d. or t. i. d. as indicated, 30 per cent. solution where there is a question of nutrition. Only chemically pure glucose should be used and distilled sterilized water. A good plan is to prepare larger quantities and use 250 c.c. (8 oz.) bottles, cotton stoppers, paraffin paper over these well down over the neck of the bottle, so that one would always have a sterile lip on the bottle to pour the solution from. Sterilize by boiling or autoclaving, then store on ice.

The method of administration is that of any arsphenamin method. Either a tube reservoir or else a 3-way stopcock with a 10 c.c. syringe can be used. In case of the latter the original bottle serves as a reservoir. The latter is more practical for private work, the first for hospital use.

Use as small a needle as you can. The smaller a needle the easier it is to enter the vein.

It is advisable to administer all the medication in glucose. I use routinely:

Tr. digitalis . . . . .	1.00000 c.c.
Morphin sulph. . . . .	0.00800 gm.
Atropin sulph. . . . .	0.00064 gm.
Glucose, 10 per cent. . . . .	250.00000 c.c.

The first is to digitalize the heart muscle and the latter to secure rest and also to prevent chills which sometimes follow any intravenous medication. The solution is heated to about 50° C., and from fifteen to thirty minutes allowed for its administration.

Remember that an ounce of prevention is worth a pound of cure. Thus do not wait with the glucose administration until the patient is nearly dead and then expect any miraculous result from it.

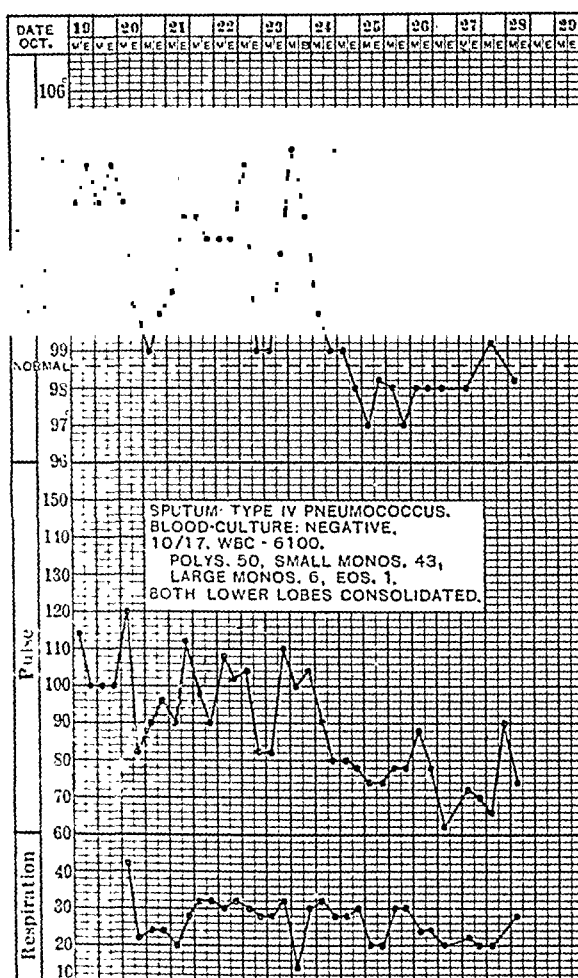


CHART II

Begin early and thus preserve the patient's strength, his natural resources, since you can do nothing specific so far as cure is concerned. Do not let the patient suffer. I think that the morphinphobia which is so impressed on the medical student has done a lot of harm when we are dealing with acute infectious diseases. The tendency is to use morphin only as a last resort, when one can see that the patient cannot live, to make his end easy. This is one of

the greatest mistakes in therapy. It should be used early, to save the patient and his natural resources, his fighting power, that he may win the victory over the infection and not be let suffer and uselessly spend his energies. It is nothing less than stupid to think that a patient will become a drug addict from the three to ten doses of morphin which he does not even know that he is getting in the glucose, but thinks that it is the glucose alone giving him the relief.

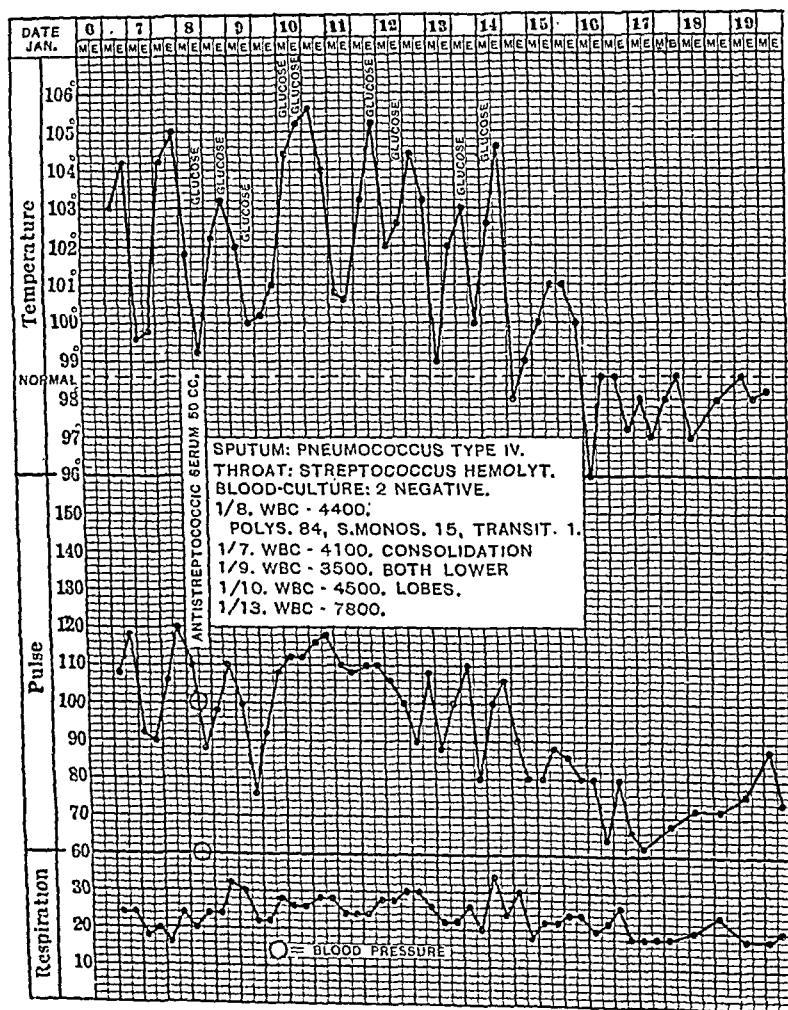


CHART III

While febrile, the patient should receive all the liquids and nourishment he will take. Fruit juices, too, are of great value.

Enemas, baths, etc., naturally should always precede the intravenous administration. After this the patient should be left perfectly quiet to rest and to sleep. A natural rest and sleep do more for the patient than all the medical armamentarium in our possession.

Our problem in pneumonia is much the same as any problem



of surgical infection. What does a surgeon do? He abides by the following principles:

1. Rest.
2. Supply of liquids and food.
3. Drainage.

Our infection is widely spread through the lung tissues, but the patient is absorbing from them just the same as the surgical case is from his area of infection. The toxic products are getting into the circulation, causing toxemia, fever, prostration and death. Through morphin and glucose you furnish rest. Through glucose you supply liquids and food to the body. The third cannot be accomplished medically. Our principle then is just the same and we can well afford to follow the surgical lead.

CONCLUSION. From the above discussion and data one can readily gather the following:

1. That the administration of glucose is without danger provided any reasonable care is used. In the 1200 administrations not a single accident developed.
2. That the patient is made comfortable and sleep is provided for him. Through this the whole organism is strengthened for the prolonged fight against the infection.
3. That the temperature is lowered.
4. That nutrition is provided for the overtaxed heart muscle without having to go through the ordinary digestive processes, storage in the liver as glycogen and reconversion into glucose again before it can be burned by the tissues. 100 to 300 calories is thus supplied to the body per each dose.
5. That a considerable amount of fluid is provided for the circulation. This together with the preceding slows the heart, producing thus artificial rest.
6. That the elimination through the kidneys and the skin is increased.
7. That practically all the medication can be supplied in the glucose, thus a much more accurate dosage can be depended on.
8. That the antipneumococcic serum type I or the antistreptococcic serum, the antitetanic serum, can be administered in this glucose medium. This is far superior to saline, for glucose will do much more than saline, thus being a much more rational medium to use as a diluent for any intravenous medication.
9. That the use of glucose is strictly a physiological measure and is to be used as such.<sup>1</sup>

<sup>1</sup> In private communication with Dr. H. O. Mosenthal, he brings out the fact that commercial glucose is preferable to the chemically pure product, which in its purification contains traces of acetic acid, and he thinks that these traces of the acetic acid have something to do with the chills that follow. His experience has been that after he had abandoned the use of the chemically pure product and resorted to commercial glucose, no chills followed. This is worth bearing in mind and publishing the results of such an investigation in the future.

# A STUDY OF THE RELATIVE TOXIC EFFECTS PRODUCED BY REGIONAL RADIATION.

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CONSTANT extension of the field of roentgen-ray therapy has brought into increasing prominence the condition of "treatment sickness," the constitutional reaction which frequently follows the use of massive doses of the hard roentgen rays. The underlying cause of this reaction is unknown. It has been ascribed to various and diverse factors, such as poisoning by toxic gases produced through the agency of the high-tension discharges, intoxication by protein decomposition products, by "roentgen toxins," by acid products, etc. As an excellent review of the theoretical aspect of the subject is found in the recent paper of Hall and Whipple,<sup>1</sup> we will not discuss this phase of the matter in detail. A factor which has, however, apparently been considered but little in investigations regarding this intoxication is one involving the question of the relative severity of symptoms following radiation of different regions of the body.

In this paper we have collected the results of a series of experiments undertaken to determine, if possible, whether by the radiation of certain portions of the body roentgen-ray intoxication is more easily produced and in more severe form than by radiation of certain other portions.

Rabbits were used in all of our experiments. Our general plan of procedure was as follows:

The animals were brought to the laboratory several days in advance, and during this period were fed on the diet (oats, celery tops and cabbage) given to all our experimentation subjects. At the end of this period 15 to 25 c.c. of blood were taken by heart punctures. This blood was used for chemical examination as described below. After being allowed to rest for from eight to twenty days, to recuperate from the loss of blood, the animals were irradiated over a single area.

A protective shield was prepared by cutting a square hole, measuring four and a half inches on a side, in the center of a large

<sup>1</sup> AM. JOUR. MED. SC., 1919, clxxxiv, 453.

piece of sheet lead having a thickness of approximately one-eighth of an inch. This shield could be placed over the animal board so that the square corresponded to areas 1, 2 or 3 on the rabbit, as shown in Fig. 1. The same shield was used in raying the thighs (area 4), but it was necessary to tie the animals' legs together in

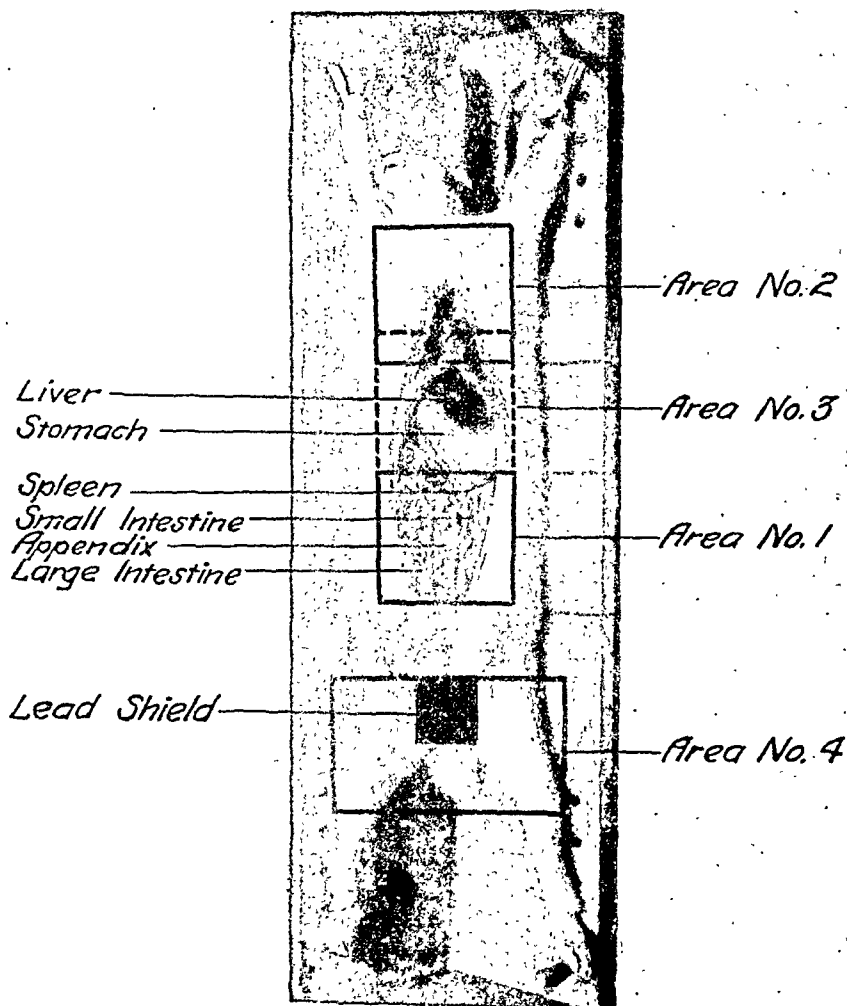


FIG. 1

order to bring them under the  $4\frac{1}{2}$ -inch hole. Since this could not be indicated in the photograph shown in Fig. 1, a square rectangle, somewhat larger than the  $4\frac{1}{2}$ -inch square, was drawn to show just what portions of the legs were irradiated. In raying areas number 5 and number 6, shown in Fig. 2, the same shield was used, but a

second piece of sheet lead was laid across the hole so that the irradiated areas measured  $2\frac{1}{2} \times 4\frac{1}{2}$  inches. All of the animal's body except the portion beneath the hole in the shield was covered with lead during irradiation. With the exception of the first dose given Rabbit No. 8, each animal received exactly the same amount of

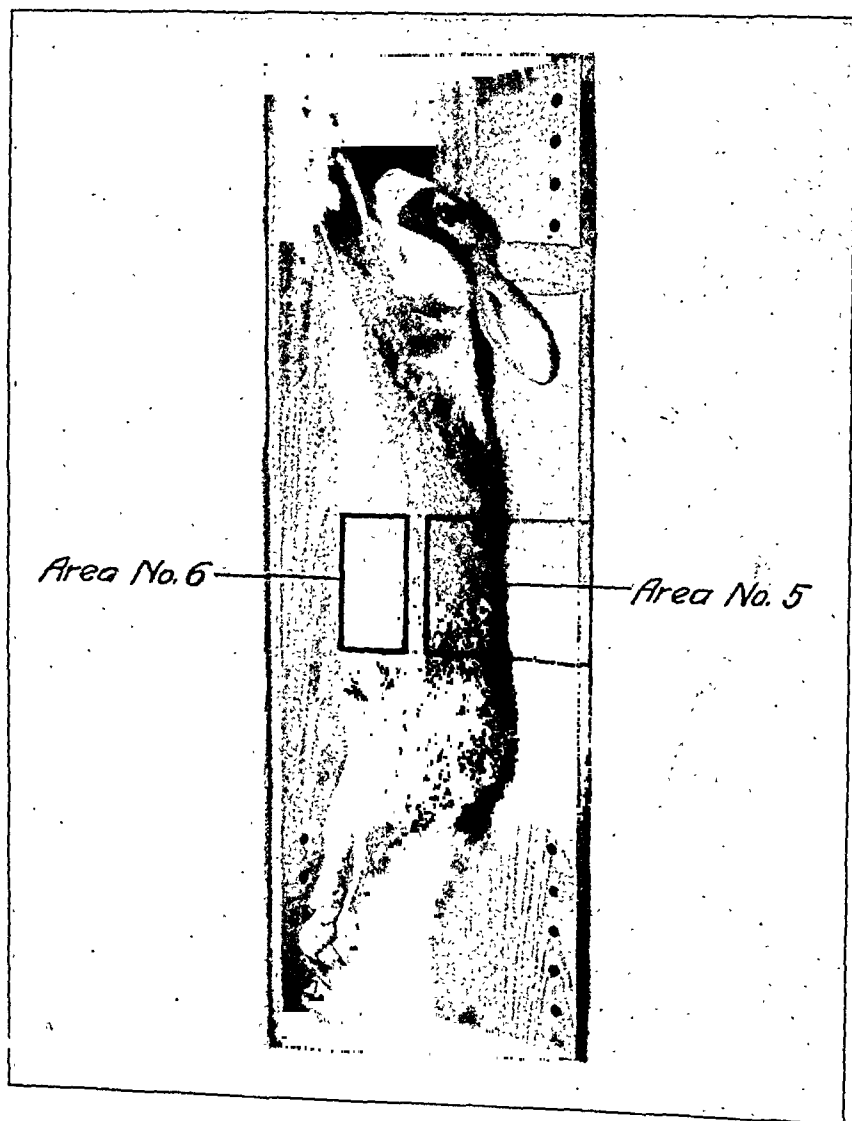


FIG. 2

irradiation as indicated by the meters measuring the electrical input to the tube. The same broad focus Coolidge tube energized by the same Snook interrupterless transformer was used for all of the work. This tube was placed with the focal spot at a distance of 8 inches from the rabbit's skin and a sheet of aluminum measuring  $2\frac{1}{2}$  mm. in thickness was used as a filter. All of the exposures were made with the tube backing up an 8-inch parallel spark gap, actually

measured between points. When the work was first started a dose of 120 ma. minutes was administered over the abdomen of rabbit No. 8, as explained later, but apparently this dose was not sufficient to produce a toxic reaction. All of the other animals received 200 ma. minutes, and rabbit No. 8 was also given this dose when exposed the second time. It was thought advisable to break up this exposure into 5 seances, each lasting four minutes, with 10 ma. passing through the tube. About four minutes were allowed to elapse between seances to prevent overheating of the tungsten target.

For the chemical examination of the blood we have used the following procedures: For non-protein nitrogen, creatinin and creatin the methods of O. Folin and Wm. H. Folin,<sup>2</sup> for fat the method of Bloor,<sup>3</sup> and for the measurement of the alkaline reserve the technic of Van Slyke and Cullen.<sup>4</sup>

As from clinical experience we were led to believe that a general systemic reaction followed heavy radiation of the abdomen more frequently than in radiation of other parts of the body, our first experiments were made to study the effects produced by exposure of the lower abdomen.

**Experiments Involving Irradiation of Animals over the Lower Abdomen (Area 1).** As will be noted from Fig. 1, the area covered in these experiments included the large and small intestines, appendix, spleen and probably a portion of the kidneys.

*Rabbit 4.* Rayed over area 1, January 11; six days after exposure the animal began to show loss of appetite, a loss of weight and a decreased output of urine; on the eighth day some diarrhea was noted. The rabbit was killed on the eleventh day, as he looked so ill that we feared he would die during the night.

*Autopsy.* The autopsy findings were as follows: The stomach was full of food and the intestines were dilated with gas. No gross abnormalities were seen in the liver, stomach, kidneys, intestines or spleen. Histologic examination of portions of the kidney and liver showed no pathologic changes.

#### RESULTS ON BLOOD OF RABBIT 4 (AREA 1).

Date.	White count.	Alkaline reserve volume percentage of CO <sub>2</sub> .	Mmg. per 100 c.c. blood.			Remarks.
			Non-protein nitrogen.	Creatinin.	Creatin.	
Jan. 4, 1920	.....	.....	51.6	1.0	4.85	Radiated Jan. 11.
" 14, 1920	5,000	65.0	60.6	1.0	4.79	
" 18, 1920	6,200	.....	65.4	1.2	4.43	
" 22, 1920	10,200	21.4	65.5	1.5		

<sup>2</sup> Jour. Biol. Chem., 1919, xxxviii, 81.

<sup>3</sup> Ibid., 1914, xvii, 377.

<sup>4</sup> Ibid., 1917, xxx, 289.

*Rabbit 5*, was rayed over area 1 on February 8. On the fourth day signs of intoxication were noted, on the twelfth day diarrhea

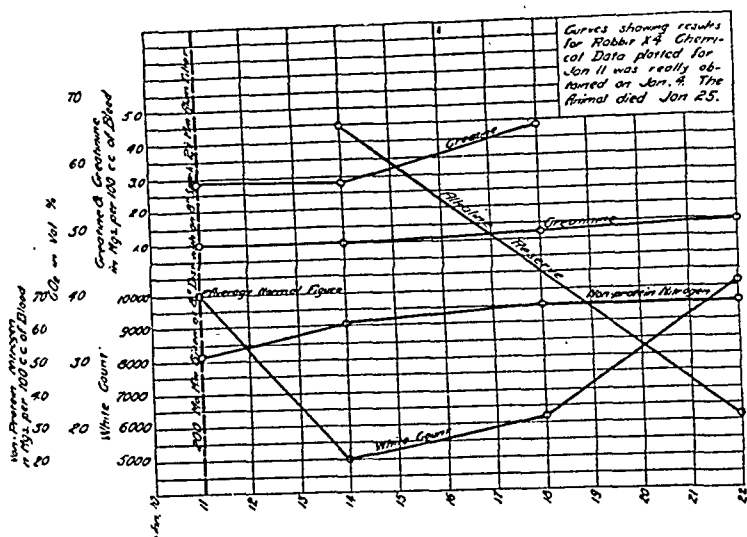


CHART I.—Results for Rabbit No. 4.

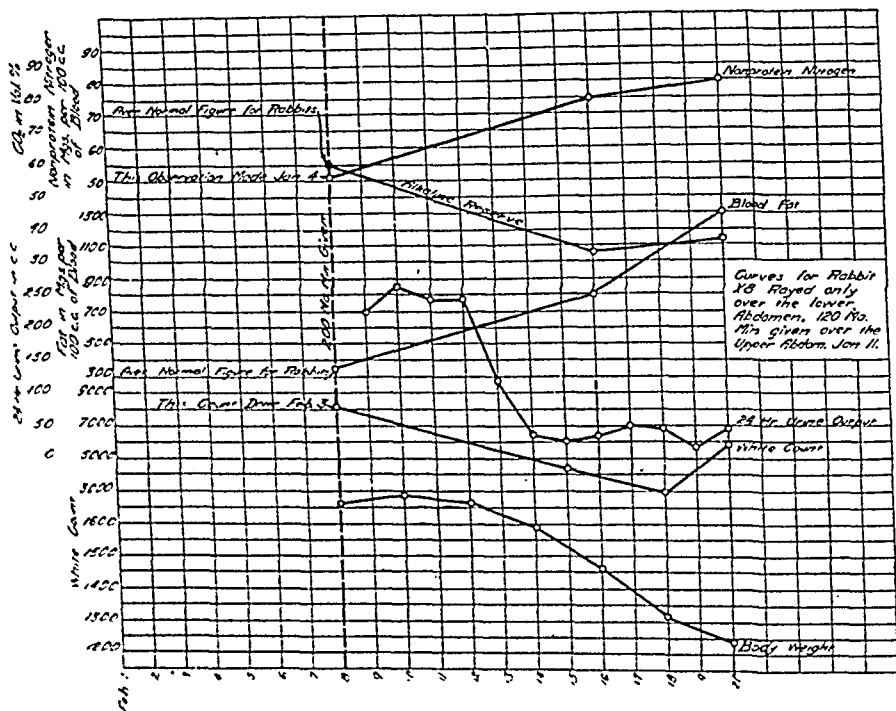


CHART II.—Results for Rabbit No. 8.

became evident and on the twenty-second day the animal was killed. The weight on the first day of the experiment was 2015 grams and on the last day 1510 grams.

An autopsy performed ten minutes after death showed the stomach full of food, the small intestine dilated with gas, the large intestine filled with liquid feces and showing a few injected areas. The kidney, liver and spleen were normal in appearance.

Histologic study of the injected areas in the large intestine revealed a complete loss of epithelium and masses of fibrin and leukocytes overlying the denuded submucosa.

#### RESULTS ON BLOOD OF RABBIT 5 (AREA 1).

Date.	White count.	Alkaline reserve; volume percentage of CO <sub>2</sub> .	Non-protein nitrogen mmg. per 100 c.c. blood.	Fat, per cent.	Remarks.
Jan. 15, 1920	.....	.....	52.0		
Feb. 3, 1920	10,800				
15, 1920	4,700	.....	.....	.....	Radiated Feb. 8.
16, 1920	.....	41.8	66.5	0.53	
20, 1920	4,900	41.4	48.7	0.52	

*Rabbit 7* was rayed over area 1 on February 8. Seven days later it was noted that the animal looked ill and would eat but little food; on the nineteenth day severe diarrhea set in and on the twenty-second day the rabbit was killed. The body weight on the first day of the experiment was 2078 grams; the weight just before death was 1734 grams. An autopsy performed a few minutes after death showed the stomach full of food, the small intestine normal in appearance and the large intestine and appendix much dilated and full of fluid feces. The appearance of the kidney, liver and spleen was normal. No injected areas were seen in any portion of the gastro-intestinal tract. Histologic studies of sections from the appendix and small intestine showed no variation from the normal.

#### RESULTS ON BLOOD OF RABBIT 7 (AREA 1).

Date.	White count.	Alkaline reserve volume percentage of CO <sub>2</sub> .	Non-protein nitrogen mmg. per 100 c.c. blood.	Fat, per cent.	Remarks.
Jan. 4, 1920	.....	.....	55.0		
19, 1920	9800				
Feb. 15, 1920	6900	.....	.....	.....	Radiated Feb. 8th.
16, 1920	.....	39.0	58.0	0.44	
19, 1920	3000				
20, 1920	4600	46.2	51.6	0.52	

*Rabbit 8* was rayed over area 1 on January 11, but only 120 ma. minutes were given. As this dose produced no apparent reaction the animal was again exposed over the same area. On February 8, on the tenth day, the usual signs of intoxication were noted; on the

fourteenth day some diarrhea appeared and on the twenty-second day the animal was killed. The body weight was 1664 grams on the first day and 1245 grams on the last day of the experiment.

An autopsy, done thirty-five minutes after death, showed the stomach full of food and much distended with gas, the small intestine dilated and the liver and kidneys normal in appearance. There were a few injected areas in the large intestine which showed a complete loss of epithelium on microscopic examination. The denuded areas of the submucosa were covered with masses of fibrin and leukocytes.

#### RESULTS ON BLOOD OF RABBIT 8 (AREA 1).

Date.	White count.	Alkaline reserve; volume percentage of CO <sub>2</sub> .	Non-protein nitrogen mmg. per 100 c.c. blood.	Fat, per cent.	Remarks.
Jan. 4, 1920	.....	.....	50.3	.....	Radiated Feb. 8.
Feb. 3, 1920	7600	.....	.....	.....	
15, 1920	4400	.....	.....	.....	
16, 1920	.....	32.8	75.0	0.8	
18, 1920	3000	.....	.....	.....	
20, 1920	5900	26.6	81.0	1.3	

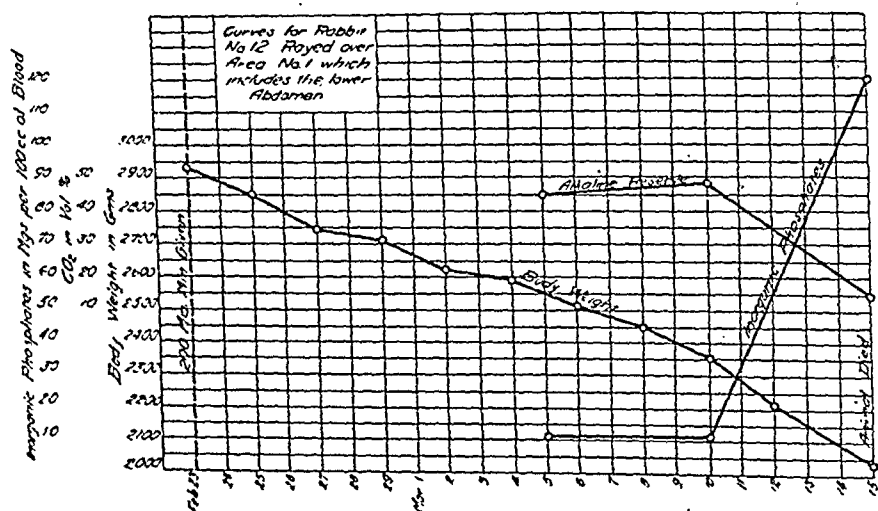


CHART III.—Results for Rabbit No. 12.

An inspection of the results presented above indicates that in rabbits irradiation of the lower abdomen gives rise to symptoms of intoxication, accompanied by rapid loss of weight and some diarrhea. Blood examination shows a rapid fall in the number of white cells, with a subsequent approach to the initial number. In Rabbits 4 and 8 there was an unmistakable increase in the non-protein nitrogen, a fall in the alkaline reserve and in the case of Rabbit 8 a rise in blood fat. The creatinin figures were unchanged. In



Rabbits 5 and 7, however, there was no increase in the non-protein nitrogen or fat and no evidence of acidosis as judged from the standpoint of the alkaline reserve. The urine of all the animals was examined at frequent intervals, but no albumin or casts could be found, nor could we find any evidence of the presence of acetone bodies even by the use of the Scott-Wilson reagent.

On account of the blood findings indicative of some acidosis in Rabbits 4 and 8 we irradiated a fifth animal (Rabbit 12) over area 1, with the object of obtaining more data on the subject. As will be seen from the results presented below the animals soon developed the usual symptoms, and toward the end of the experiment gave evidence of great reduction in the alkaline reserve, accompanied with a marked retention of phosphates, a result of interest, in view of the findings of Marriott and Howland on the relation between phosphate retention and acidosis in some cases of nephritis.

The urine was at all times free from albumin and casts and gave no reaction for acetone.

*Rabbit 12* was rayed over area 1 on February 23. Eight days later the animal developed the usual symptoms of intoxication and was killed on the twenty-third day. The weight at the beginning of the experiment was 2930 grams, at the end of the experiment 2030 grams.

March 5. Examination of the blood gave the following results: Alkaline reserve, 45 volumes per cent  $\text{CO}_2$ ; inorganic phosphates of the plasma calculated as phosphorus, 3.4 mg. for 100 c.c. plasma.

March 15. Alkaline reserve, 16, inorganic phosphate of plasma, 40.0 mg., non-protein nitrogen, 232 mg. for 100 c.c.; fat, 2.6 per cent.

**Experiments Involving Irradiation of Animals over the Upper Portion of the Abdomen (Area 3).** This experiment was undertaken to determine whether by irradiation of the upper abdomen close to the level of the costal margin it is possible to produce an intoxication similar to that produced by raying the entire abdomen.

The area exposed included the entire thorax and the upper abdominal viscera, viz., the liver, spleen, stomach and a portion of the small intestine.

Only one animal was observed (*Rabbit 16*). The symptoms were identical with those occurring in the subjects used in Experiment 1, involving rapid loss of weight, diarrhea and prostration.

The weight of the animal on the first day of the experiment was 2300 and on the twenty-third day 1800 grams.

No chemical data were obtained.

**Experiments Involving Irradiation of Animals Over the Chest and Neck (Area 2).** As will be noted from Fig. 1 the area covered in these experiments included the heart, lungs and thyroid.

*Rabbit 15* was radiated February 29. The animal continued in good condition for fifteen days, when a slight loss of weight was noted. Some days later a skin-burn, with marked contraction and loss of

hair, was noted over the radiated area. The animal was kept under observation until April 15, but up to this time showed no symptoms.

The body weight on the first day of the experiment was 2700 grams, on the last day 2720.

The following results were obtained on a sample of blood taken at the end of the experiment:

Non-protein nitrogen, 58 mg. per 100 c.c. of blood.

Alakline reserve, 47 volumes per cent.  $\text{CO}_2$ .

*Rabbit 17* was rayed over area 2 on March 18. He remained in good condition until April 15, when the experiment was concluded.

The weight on the first day of the experiment was 2510 grams and on the last day 2650 grams.

The following results were obtained on a sample of blood taken at the end of the experimental period:

Non-protein nitrogen, 53 mg. per 100 c.c. of blood.

Alkaline reserve, 52 volumes per cent.  $\text{CO}_2$ .

*Rabbit 24* was irradiated on March 20 over area 2 and kept under observation until April 15. During this period no symptoms suggestive of intoxication developed.

The body weight on the first day of the experiment was 2410 grams and on the last day 2398 grams.

The following results were obtained on a sample of blood taken at the end of the experimental period:

Non-protein nitrogen, 57 mg. per 100 c.c. of blood.

Alkaline reserve, 48 volumes per cent.  $\text{CO}_2$ .

**Experiment Involving Irradiation over the Thighs (Area 4).** This experiment was done to study the results of irradiation over an area containing no viscera. In the one animal used no reaction was obtained. After a period of three weeks a skin-burn developed, accompanied by contraction and loss of hair. Otherwise the animal appeared to be in good condition when observation was discontinued four weeks after exposure.

**Experiments Involving Irradiation of Animals over the Anterior and Posterior Portions of the Abdomen (Areas 5 and 6).** These experiments were carried out to determine whether there might be any difference in the toxic symptoms produced by radiating the anterior and posterior portions of the abdomen of the rabbit.

The animals were placed in the position illustrated in Fig. 2 and the standard dose applied to areas 5 and 6. The only viscera exposed in area 5 were the kidneys, although it cannot be definitely said that all of the intestines and the spleen were excluded. Only intestine was included in area 6.

*Rabbit 10* was irradiated over area 5 on February 23. On the third day the animal looked ill and on the fourth day diarrhea set in. The animal was bled from the heart on the eighth, twelfth and eighteenth days. A hemorrhage resulting from the last heart puncture caused death.

Weight on the first day of the experiment was 2025 grams and on last day 1470 grams.

## RESULTS ON BLOOD OF RABBIT 10.

Date.	White count.	Alkaline reserve; volume percentage of CO <sub>2</sub> .	Non-protein nitrogen mmg. per 100 c.c. blood.	Fat, per cent.	Remarks.
Feb. 18, 1920	10,600	.....	.....	.....	Radiated over area 5, Feb. 23.
Feb. 28, 1920	8,600	.....	.....	.....	
Mar. 5, 1920	5,400	41.3	44.0	0.57	
9, 1920	6,000				
10, 1920	.....	47.2	50.5	0.67	
23, 1920	.....	32.8	53.0		

*Rabbit 11* was irradiated over area 6 on February 23. Here the reaction was much delayed. The animal continued well until the eighteenth day, when it began to lose weight. On the twentieth day a serious diarrhea developed and on the morning of the twenty-second day it was found dead.

Weight on the first day of the experiment was 2165 grams and on the last day 1560 grams.

## RESULTS ON BLOOD OF RABBIT 11.

Date.	White count.	Alkaline reserve; volume percentage of CO <sub>2</sub> .	Non-protein nitrogen mmg. per 100 c.c. blood.	Fat, per cent.	Remarks.
Feb. 14, 1920	9200	.....	58.0	.....	Radiated over area 6, Feb. 23.
28, 1920	9400				
Mar. 5, 1920	5600	31.8	44.0	0.5	
Mar. 10, 1920	5000	32.0	60.0	0.8	

On consideration of the findings, in which our animals showed marked loss of weight, with the accompaniment of blood changes indicative of some acidosis, it occurred to us that the objection might be made that these blood changes could be produced simply by a condition of undernutrition. It should be pointed out, however, that our animals invariably ate all the green food provided for them but refused to touch the oats which previously had been well liked, and that at autopsy their stomachs were always full. However, in order to obtain direct evidence we kept two rabbits for a period of twelve days on a daily intake of 100 grams of lettuce, no other food except water being provided. As a result of this treatment the animals lost weight, but examination of a sample of blood taken at the end of the period gave no evidence of acidosis.

*Rabbit 25* was fed on a daily ration of 100 grams of lettuce for

twelve days; weight on the first day was 2960 grams and on the twelfth day 2790 grams.

Examination of the blood on the twelfth day gave the following results: Non-protein nitrogen, 48 mg.; alkaline reserve, 49 volumes per cent.  $\text{CO}_2$ ; fat, 0.45 per cent.

*Rabbit 26* was fed on a daily ration of 100 grams of lettuce for twelve days. Weight on the first day 2580 grams and on the twelfth day 2281 grams.

On the twelfth day examination of the blood gave the following results: Non-protein nitrogen, 51 mg.; alkaline reserve, 50 volumes per cent.  $\text{CO}_2$ ; fat, 0.70 per cent.

**Discussion.** In considering the results of the experiments described above it will be noted that toxic reactions were produced only in the animals exposed over areas in which some portion of the intestine was included, and, furthermore, that severe intoxications were invariably produced by irradiation of these areas. Thus even the rabbit exposed over area 5, which probably contained only a small portion of intestine, developed toxic symptoms after a rather long latent period, while a particularly severe reaction followed irradiation over area 6, which contained none of the viscera other than portions of the intestinal tract. On the other hand, animals irradiated over the thighs and over the neck and chest continued in good condition and showed absolutely no symptoms, though kept under observation for a period of several weeks. Our results would appear to confirm the findings of Hall and Whipple, who state that they believe injury to the intestinal epithelium to play no small part in the systemic reactions following exposure to the roentgen rays. These investigators, who worked with dogs, describe the same small isolated areas of epithelial destruction noted by us. These patches, which could be readily identified in the gross by small injected areas in the intestinal wall; were frequently, but not invariably, found by us at autopsy; in fact, in some of the rabbits in whom the reaction was particularly severe no such abnormality could be detected. In view of the inconsistency of these anatomic lesions we feel some hesitation in attributing much importance to them; in fact, we are inclined to suggest the hypothesis that they are, perhaps, the result rather than the cause of the intoxication.

The inhalation theory of roentgen-ray intoxication advanced by Wilbert<sup>5</sup> in 1899 and by Pfahler<sup>6</sup> in 1916 is hardly consistent with our findings. If the gases produced by the high-tension discharge from the leads running to the tube were at all instrumental in producing the reactions observed the animals irradiated over the chest and over the hind legs should have shown the same symptoms as those irradiated over the abdomen, since they were all treated in the same manner and all inhaled the same gases.

<sup>5</sup> Philadelphia Med. Jour., 1899, iii, 1014.

<sup>6</sup> Am. Jour. Roent., 1916, iii, 310.

Linser and Sick<sup>7</sup> and Engel<sup>8</sup> claim that the intoxication results from "roentgen toxin" produced in the blood. All of the blood passes through the heart and pulmonary circulation; it is spread out in numerous fine capillaries in the lungs and should undoubtedly receive thorough irradiation during an exposure of the chest. If we are to accept the "roentgen-toxin" theory, irradiation of the chest should produce a reaction as quickly as irradiation of the abdomen, a postulate which has not been borne out by our results. Linser and Helber,<sup>9</sup> Rosenstern<sup>10</sup> and Warthin<sup>11</sup> believe that the intoxication results from a roentgen-ray nephritis. The kidneys of some of the rabbits who had received heavy abdominal exposures were examined histologically by Dr. J. H. Wright, who reported the entire absence of lesions. Frequent urinary examinations invariably gave negative results for albumin and casts, nor could we, except in the case of one animal (Rabbit 12), obtain evidence of any retention of nitrogen, if we may judge by the figures obtained on the determination of non-protein nitrogen in the blood. Our results, therefore, do not offer evidence of the existence of a roentgen-ray nephritis but rather are in accord with the results of Hall and Whipple, who found no abnormality in the kidneys of dogs after irradiation. Much work has been done on the effect of irradiation on enzymes,<sup>12</sup> and especially on the enzymes of the gastro-intestinal canal.<sup>13</sup> In view of the fact, however, that the intoxication produced in animals progresses slowly over a period of two or three weeks, it would appear that this intoxication must be produced by an inhibition of cellular function rather than by a chemical change in the digestive juices. Most but not all of the rabbits who received heavy exposures over the intestines gave evidence of the presence of an acidosis, as shown by a fall in the alkaline reserve and a rise in the fat and in the inorganic phosphate of the blood. This condition we feel sure cannot be due to starvation, for the animals ate lettuce and celery in generous amounts up to the day of death. The fact is not without interest that these animals refused to touch oats, an acid food, but partook freely of lettuce and celery, which is rich in alkaline salts.

In view of the relatively small number of animals used, it is perhaps premature to attempt to obtain too rigid a theoretical basis for our findings; but we would call attention to the fact that acidosis based on intestinal disturbances has been observed chemically many times. Edsall,<sup>14</sup> in 1902, described a case of coma with acidosis which was apparently due to intestinal upset; much has been written about the occurrence of acidosis as a result of intestinal intoxication in children. The occurrence of acidosis in Asiatic cholera has been

<sup>7</sup> Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 288.

<sup>8</sup> Deutsch. med. Wehnschr., 1907, xxxiii, 22.

<sup>9</sup> Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 479.

<sup>10</sup> Munchen. med. Wehnschr., 1906, liii, 1063.

<sup>11</sup> Am. Jour. Med. Sc., 1907, cxxxiii, 736.

<sup>12</sup> Ztschr. f. Krebsf., 1904, ii, 171.

<sup>13</sup> Am. Jour. Physiol., 1914, xxxv, 224.

<sup>14</sup> Philadelphia Med. Jour., June 28, 1902.

described by Sellards,<sup>15</sup> who, however, believes this phenomenon to be the result of the nephritis which has been found so frequently in his cholera cases.

The experiments recorded above were originally undertaken in an attempt to throw some light on the obscure cause of "treatment sickness." Before attempting to apply the results of our animal experiments to a discussion of this intoxication in the human subject, the fact must be borne in mind that the dose received by each area of the rabbit's body was about five times the dose usually given any one portion of the body of a patient; where the cross-fire method is used, however, it is conceivable that an internal organ might receive as much irradiation as did the internal organs of our rabbits; but, again, consideration must be taken of the fact that the area used in our experiments was large enough to cover half of a rabbit's abdomen, but would, of course, include only a small portion of the abdomen of a man.

A further difference in clinical "treatment sickness" and in the intoxication produced in animals is the fact that in the human subject the symptoms usually appear a few hours after exposure and last but a few days, whereas in the case of rabbits absolutely no objective symptoms appear for several days after irradiation; but once started, the symptoms become progressively severe.

Our results would suggest, although they by no means prove the fact, that the severe systemic reactions encountered after irradiation of the abdomen in patients may be in part at least caused by an acidosis. Careful and extensive work with clinical material is, of course, necessary before this hypothesis can be considered seriously. Such an hypothesis does not, and in fact need not, attempt to explain the severe reaction frequently observed after irradiation of tumors of the chest and of the extremities, for in cases in which large growths are caused to rapidly shrink by exposure to the roentgen-ray it is highly probable that toxic bodies of a protein nature may be discharged into the circulation.

We wish to express our appreciation of the valuable suggestions offered by Dr. George W. Holmes and of the kind coöperation of Dr. J. H. Wright, who reported on our histologic sections.

**Summary.** 1. A definite massive dose of roentgen-rays administered to the body of a rabbit produces a severe systemic reaction and death only when some portion of the intestinal tract lies within the irradiated area.

2. It is possible to produce a definite acidosis (lowering of the alkaline reserve) in rabbits by administering a heavy dose of roentgen-rays over the abdomen. Such animals give no evidence of suffering from a "roentgen-ray nephritis."

3. The results suggest the hypothesis that acidosis may be a factor in "treatment sickness" following abdominal irradiation.

<sup>15</sup> Principles of Acidosis, 1917.

<sup>16</sup> Am. Jour. Roent., 1916, iii, 356.

EPIDEMIC ENCEPHALITIS: INCLUDING A REVIEW OF 115  
AMERICAN CASES.

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DURING the past three years, in the wake of a world-wide epidemic of respiratory disease, there have appeared an unusual number of cases presenting the symptomatology of a disseminated encephalitis. A brief study at this time of the etiology, pathology, symptomatology, prognosis and treatment as revealed by an analysis of 115 American cases, inclusive of 15 personal cases, should be of interest, for it would seem from a survey of the literature and from personal experience that epidemic encephalitis is being repeatedly misdiagnosed as poliomyelitis, botulism, brain abscess, cerebral hemorrhage, thrombosis, embolism, meningitis, acute paralysis agitans, etc., and that the data had not been at hand on which to evaluate the symptomatology of the disease.

The advent of a "new disease" naturally aroused the curiosity of students of medical history. It was soon learned that the supposed "new disease" was centuries old and had appeared repeatedly under different names, but with similar symptoms in association with previous respiratory epidemics. Crookshank<sup>1</sup> opens his article with an epigrammatic quotation from Bouvier,<sup>2</sup> written in 1837, which is worth repeating, and which summarizes, in an inimitable manner, the results of Crookshank's investigations into the history of the disease: "On l'a dit justement, les mêmes questions renaissent à chaque épidémie catarrhale et leurs solutions diverses se reproduisent chaque fois à peu près les mêmes." Different names have been applied in the past as in the present, but the symptoms were much the same. The first cases in the present epidemic were described by von Economo<sup>3</sup> in Austria in 1917; by Netter<sup>4</sup> in Paris in 1918; by Wilson<sup>5</sup> and others in England in 1918; by Tilney<sup>6</sup> and Riley in New York, and Bassoe<sup>7</sup> in Chicago, early in 1919.

<sup>1</sup> Boston Med. and Surg. Jour., 1919, clxxxii, 34.

<sup>2</sup> Ann. d'hyg. pub. et de méd. Legale, 1837.

<sup>3</sup> Wien. klin. Wchnschr., 1917, xxx, 581.

<sup>4</sup> Bulletin de l'académie de médecine, Paris, May, 1918, and November, 1918.

<sup>5</sup> London Lancet, 1918, ii, 91.

<sup>6</sup> Neurological Bulletin, 1919, vol. ii.

<sup>7</sup> Jour. Am. Med. Assn., 1919, lxxii, 971.

*Etiology.*—The cause of the disease is unknown and the opinions of those who have attempted etiological investigations are at variance. In 1917 von Wiesner<sup>8</sup> claimed to have produced a hemorrhagic encephalitis by inoculating into the brains of apes a diplococcus obtained from one of von Economo's cases, but without reproducing the histological pictures found in man. Marinesco<sup>9</sup> and McIntosh saw in and isolated from the meninges and pons two types of organisms, namely, a thick, Gram-positive, anaërobic bacillus which was pathogenic for mice and a diplococcus which was occasionally associated with the bacillus. Strauss,<sup>10</sup> at the Rockefeller Institute, reproduced the disease in apes with filtered nasopharyngeal secretions and maintained that the cause was a filtrable virus. May we not here again be up against the same *impasse* that has prevailed in poliomyelitis: the Flexner filtrable virus—globoid bodies—on the one hand and the Rosenow streptococcus with the "globoid bodies" considered merely as variants of a streptococcus, on the other hand?

One of us isolated a green streptococcus from the blood of a case (No. 12, Tables II and III) which was recovering from influenza with bronchopneumonia, and which was at the time developing a typical epidemic encephalitis with lethargy and diplopia. The organism was agglutinated by the patient's serum only and was not agglutinated by other sera. The patient's serum did not agglutinate laboratory strains of diplococci and streptococci. The organism had the cultural characteristics of the organism which was frequently isolated from the blood and lungs in the epidemic of influenza in Omaha in 1918 (Dunn<sup>11</sup>). The organism died out before animal experiments could be instituted and repeated cultures later failed to recover the organism. The immediate bearing of influenza on epidemic encephalitis is a moot question. In the 115 cases here analyzed 36 gave a history of a respiratory infection within one year (average time two months) prior to the onset of the encephalitis. The relative infrequency of encephalitis in a pandemic of influenza is noteworthy. On the contrary the appearance of encephalitic disease chiefly at the periods of a world-wide respiratory infection is suggestive. Draper<sup>12</sup> seemed inclined to assume that a close relationship exists between epidemic encephalitis and poliomyelitis, the former being a possible variant of the latter. It is to be noted that in 12 of our personal cases 5 gave a history of repeated severe tonsil infections; of the other infectious diseases, 2 had had typhoid, 2 diphtheria, 2 inflammatory rheu-

<sup>8</sup> Klin. Wehnschr., 1917, xxx, 933.

<sup>9</sup> L. G. B., London, 1918, p. 121.

<sup>10</sup> Jour. Am. Med. Assn., lxxii, 20, 1493; New York Med. Jour., 1919, cix, 772.

<sup>11</sup> Observations on an Epidemic of Bronchopneumonia in Omaha, Jour. Am. Med. Assn., December 28, 1918, p. 2128.

<sup>12</sup> L. G. B., London, 1918, No. 121, p. 62.



matism, 1 scarlet fever, 1 chorea, 1 pleurisy, 1 tuberculosis of the knee.

**Symptomatology.** The symptomatology of epidemic encephalitis is protean. When one considers that it is the brain-stem—the great switchyard of the central nervous system—which is the site of predilection of the virus the multiplicity of symptom complexes is explained. Even microscopic lesions in such an area as the mesencephalon may be fraught with much symptomatic import. All parts of the brain-stem and cerebrum, however, are open to attack. We have found it useful from a clinical standpoint to arrange the more or less characteristic symptoms in groups or types: (1) Polioencephalitic; (2) lethargic; (3) Parkinsonian; (4) cataleptic; (5) meningitic; (6) cerebral; (7) polyneuritic; (8) myelitic. We have endeavored to place these groups on a pathological and anatomical basis. We confess that the grouping is artificial, and that, on account of the multiplicity and disseminated character of the lesions it cannot be a hard and fast one, but in the study and recognition of cases we have found it helpful. The classification has been arranged from an analysis of the symptoms of 115 cases, with acknowledgment to MacNalty,<sup>13</sup> Tilney and Riley (*loc. cit.*) and others. The syndromes always overlap, so that a case may easily find itself in two or more groups. For example, J. C. (Case No. 9, Tables II and III) could have been placed at different times in either of two groups: In the cerebral group on account of Jacksonian epilepsy, motor aphasia and right-sided spasticity; in the agitans group on account of tremor, spasticity and the Parkinsonian mask. Careful correlation of symptom groupings with subsequent pathological study may throw some light on cerebral localization and on the function of the "dark" areas of the central nervous system. Five of the 15 personal cases were classified as polioencephalitic (1 superior); 3 lethargic; 1 Parkinsonian; 1 meningitic; 4 cerebral (2 convulsive, 1 psychotic, 1 epileptomaniacal), 1 polyneuritic. It must be emphasized that the group to which a given case is assigned depends greatly on the time in the course of the disease at which the patient is grouped. At one period a case may fall clearly into the polioencephalitic at a later period into the lethargic group. We have excluded a poliomyelitic group, for neither in our own cases nor in the literature do we find any cases which are sufficiently frank to be called poliomyelitic. Tilney and Riley's (*loc. cit.*) case is exceptional. The lethargy in this case would not seem typical, and one case is not sufficient grounds for a separate type without pathological corroboration. We feel that the posterior poliomyelitic type can quite well be classified, temporarily at least, as polyneuritic.

<sup>13</sup> L. G. B., London, 1918, No. 121.

TABLE I.—SYMPTOMATOLOGY. CLASSED ANATOMICALLY.

Type.	Symptom.	100 cases.	15 cases.	Part.
Polioencephalitic	Cranial nerve palsies:	..	..	Midbrain,
Ophthalmoparetic	III . . . . .	60	6	pons and
	IV . . . . .	2(?)	0	medulla.
	V . . . . .	7	3	
	VI . . . . .	34	6	
	VII . . . . .	12	5	
	VIII . . . . .	4	2	
	IX . . . . .	2	0	
	X . . . . .	1	0	
	XI . . . . .	0	0	
	XII . . . . .	11	2	
	Eyes:			
	Diplopia . . . . .	50	8	
	Anisocoria . . . . .	25	4	
	Ptosis . . . . .	20	0	
	Lack of light and accommoda-			
	tion reflex . . . . .	12	4	
	Sluggish pupils . . . . .	20	4	
	Retinal changes . . . . .	10	2	
	Swallowing . . . . .	13	0	
	Vomiting . . . . .	8	1	
	Polypnea . . . . .	1	2	
Lethargy	Lethargy . . . . .	69	10	Pituitary,
	Insomnia . . . . .	16	4	thalamus,
				iter and
				cerebrum.
Cataleptic	Catalepsy . . . . .	20	6	Cerebellum.
	Vertigo . . . . .	19	5	
	Nystagmus . . . . .	17	1	
	Ataxia . . . . .	4	2	
Meningeal	Headache . . . . .	47	10	Meninges.
	Rigidity neck . . . . .	12	1	
	Delirium . . . . .	24	6	
	Kernig . . . . .	3	3	
	Tache . . . . .	1	0	
Paralysis agitans	Parkinsonian mask . . . . .	9	3	Lenticular
	Spasticity . . . . .	..	4	nucleus.
	Festination . . . . .	3	0	
Myelitic	Tremor . . . . .	30	5	
	Bladder . . . . .	15	4	Cord
	Reflexes disturbed . . . . .	25	7	
	Babinski . . . . .	14	7	
	Reflexes absent . . . . .	2	2	
	Clonus . . . . .	5	4	
Epileptomaniacal	Convulsions . . . . .	0	2	Cerebrum.
	Paralyses . . . . .	0	1	
	Asynergies . . . . .	20	0	
Psychotic	Epileptiform attacks . . . . .	..	3	
	Hallucinations . . . . .	..	3	Cerebrum.
	Illusions . . . . .	..	3	
	Depression . . . . .	9	..	
Polyneuritic	Delirium . . . . .	24	7	
	Pain in extremities . . . . .	23	3	
	Sensation disturbed . . . . .	..	1	
	Paresthesias . . . . .	6	3	
	General symptoms:			
	Epistaxis . . . . .	1	1	
	Cervical adenitis . . . . .	..	2	
	Tachycardia . . . . .	..	1	
	Weight loss . . . . .	..	5	
	Appetite increased . . . . .	..	6	
	Fever . . . . .	43	13	
	Perspiration . . . . .	6	15	
	Hiccough . . . . .	5	0	
	Tears . . . . .	4	0	

Table I has been made to show the relative frequency of individual symptoms and their grouping. This table is instructive from the symptom incidence as well as from the localization standpoint. The anatomical localization of symptoms in some instances is far from settled. Lethargy is attributed to pituitary involvement by Cushing<sup>14</sup> and Climenko<sup>15</sup> and to the thalamus by von Economo (*loc. cit.*), MacNalty (*loc. cit.*) and Flexner.<sup>16</sup> We have assigned catalepsy to the cerebellum because it is a manifestation of disturbance in that extrapyramidal muscle tonus controlling apparatus of which the cerebellum forms an important part. Vertigo, nystagmus and ataxia are grouped under the cerebellum also because they arise as frequently in cerebellar as in disturbances elsewhere. Disturbed bladder and deep and superficial reflexes are attributed to the cord because they occur in cord diseases, but with full realization that some of them occur quite as frequently from lesions elsewhere. The groups or types, as shown in Table I, are useful merely in calling attention to symptom-complexes and in facilitating their recognition.

**Special Symptoms.** Certain of the more prominent symptoms should receive comment. The incidence of what we consider the less important symptoms can be seen by consulting Table I.

**Ocular Disturbances.** Disturbance in the third and sixth nerves is far and away the most common symptom occurring in epidemic encephalitis. In the 115 cases third nerve palsies were present in 63 cases and sixth nerve in 39. Diplopia was the initial symptom in 19 cases and was recorded in 55 cases. Ptosis was present 21 times. Diplopia is often an evanescent and baffling symptom, for although the patient may maintain that he sees double, yet the oculist cannot demonstrate the muscles involved. We believe that this symptom is more common than the statistics would indicate, because invariably in our own cases, when the question was brought up squarely to the patient or to the relatives the presence of visual disturbances was substantiated. The absence of the fourth nerve involvement is striking in spite of the close anatomical proximity of its nucleus to that of the third. Is this due to its short and protected course on the dorsum of the brainstem? *In what may be considered as a diagnostic triad of the disease viz., (1) ocular symptoms, (2) lethargy and (3) a negative or typically atypical spinal fluid, ocular symptoms hold first place.*

**Other Cranial Nerves.** The sensory portion of the fifth was involved 9 times in 115 cases. Apparently the motor portion of the fifth is rarely involved, and may not this be explained, in some instances at least, by its long mesencephalic sensory root which extends along the floor of the iter in close proximity to the nuclei of the third

<sup>14</sup> Diseases of the Pituitary, Philadelphia, 1912, pp. 101-102.

<sup>15</sup> New York Med. Jour., March 27, 1920.

<sup>16</sup> Jour. Am. Med. Assn., March 27, 1918.

nerve which are so commonly involved? In one of our cases the onset was associated with pain on the right side of the head and face, which soon shifted to the left side, and which was so severe that morphin was required. The patient did not sleep for seven days. Later a seventh nerve paralysis developed. As the pain subsided lethargy appeared. The development of a corneal ulcer on the left side, a left peripheral seventh paralysis, an involvement of the left chorda tympani and a left nerve deafness in this case are noteworthy. In the presence of the above symptoms, and with a spinal fluid showing 24 cells per cubic millimeter, globulin plus 2, a mild paretic gold chloride curve, negative cultures and smears and a negative Wassermann in both spinal fluid and blood, a *localized meningitis of unknown etiology* was assumed until lethargy appeared. This case would be explained by the meningoradiculitis conception recently advanced by Bassoe.<sup>17</sup> Fifteen of the cases had paralysis of the seventh nerve. The paralysis was generally peripheral in type and unilateral. The tendency of seventh nerve paralysis is to clear up slowly, requiring from four to five months. Involvements of the other cranial nerves (first, second, ninth, tenth, eleventh and twelfth) seems of minor diagnostic significance (13 cases out of 115). (See Table I.)

*Polypnea* occurred in 3 cases, 2 of them in our own series. In one of our cases (No. 5) a respiratory state of 60, which seemed to be of respiratory center origin, was maintained for thirty-six hours. The respirations in the other case (No. 10) were 80 to 100 per minute; they suggested irregular diaphragmatic and abdominal spasms (myoclonus) and occurred in attacks which were associated with extreme suffering, necessitating the use of morphin. This symptom, although rare, merits special attention, because when present it dominates the clinical picture.

*Lethargy* occurred in 79 cases and was the first symptom noted in 34 cases. It was preceded by insomnia in 4 cases. The degree of lethargy was variable. In extreme cases it may approximate a coma vigil. Usually the patients can be aroused and appear dazed as if awakening from a deep sleep. The patients, when aroused, can answer questions, but soon relapse into their stupor. The dazed, blank, expressionless stare is quite characteristic. The lethargy in most instances does not differ from a normal deep sleep, but on awakening a normal expression is absent. The patients are negativistic and their faces are dead. The lights of intelligence and interest are out or burn low.

*Catalepsy* and *catatonia* would seem to be more common than it appears from the literature, occurring in 6 out of 15 cases in our personal series and in only 20 out of the 100 cases collected from American literature. Increased muscle rigidity is common and *flexibilitas cerea* was noted 4 times in our 15 cases.

<sup>17</sup> The Delirious and Meningoradicular Type of Epidemic Encephalitis, Jour. Am. Med. Assn., April 10, 1920, lxxiv, 1009.

TABLE II.—GENERAL SYMPTOMS IN EPIDEMIC ENCEPHALITIS.

Sex, age, name, date.	General.	Medulla.	Cerebrum, iter.	Cerebellum.	Meninges.	Lenticular nucleus.	Cord periphery.
1.—U. H. (M.), 53 years Feb. 3, 1920	Weight loss; fever; perspire; chilly	...	Apathy; insomnia	Nystagmus vertigo	Headache	Mask.	Oppenheim left; Gordon left.
2.—F. P. K. (M.), 40 years Feb. 4, 1920	Weight loss; nosebleed; fever	...	Drowsy; insomnia	...	Headache	...	...
3.—F. S. B. (M.), 56 years Jan. 8, 1920	Weight loss	...	.....	Vertigo	Headache	...	Knee-jerks, plus 3; Romberg.
4.—M. H. (F.), 20 years Jan. 23, 1920	Temperature 100°; cervical nodes enlarged	...	Insomnia; nervous delirium	...	Headache; photophobia; Kernig	...	Oppenheim; splinter loss; numbness in hands; chest; clonus; knee-jerks. Pain in right arm.
5.—O. S. H. (M.), 50 years Feb. 27, 1920	Grippe, 101°	...	Lethargy; delirium	...	....	...	...
6.—J. D. (M.), 50 years Oct. 19, 1919	.....	Polypnea	Coma; delirium; lethargy; clonus arms	Nystagmus; vertigo	Headache	...	Twitching arms; abdominal clonus; Oppenheim right.
7.—J. S. (F.), 5 years May 23, 1919	Chilly; fever; adenitis; scaling hands; nausea; perspiration	...	Convulsions; Jacksonian epilepsy; coma	...	Headache; photophobia irritable	...	Twitching; Oppenheim; Babinski; knee-jerks.
8.—H. H. (M.), 44 years Apr. 3, 1919	Perspiration; fever; carphologia; appetite increased	...	Lethargy; delirium; sensation?	Catalepsy	Headache; rigid neck	Tremor; mask; spastic	Babinski.
9.—J. C. (M.), 55 years Aug. 20, 1919	Dyspnea; aphonia; perspiration	...	Right-hand spasm; lethargy; motor aphasia; Jacksonian epilepsy	Vertigo; ataxia; catalepsy	Headache	Scanning speech; mask; spastic	Babinski in right; ankle-clonus; right arm reflex, plus 2.
10.—H. W. (M.), 40 years Feb. 17, 1920	Fever	Polypnea	Delirium; hallucinations; illusions	...	Headache; Kernig	...	Pain in legs; Oppenheim; incontinence; Babinski in right; knee-jerks and ankle-jerks.
11.—E. L. C. (M.), 18 years Jan. 27, 1920	Perspiration; appetite increased	...	Delirium; hallucinations; illusions; loss of memory	Catalepsy	Photophobia	...	Oppenheim; Babinski; Gordon; clonus.
12.—Mrs. B. (F.), 45 years Feb. 2, 1920	Tachycardia; nephritis; influenza	...	Illusions; delirium; lethargy; hallucinations	Catalepsy	Kernig	Spastic	Babinski.
13.—M. M. (M.), 34 years Apr. 1, 1919	Chills; fever; carphologia	...	Lethargy; delirium	Vertigo	Photophobia; headache	Tremor	Incontinence.
14.—I. F. Feb. 1, 1920	Fever; pneumonia	...	Lethargy	Right tremor	....	...	...
15.—G. V. (M.), 25 years Jan. 25, 1920	Perspiration; fever	...	Jacksonian epilepsy	Right tremor	....	...	Babinski in right; arm-clonus in right.

TABLE III.—CRANIAL NERVE SYMPTOMS IN EPIDEMIC ENCEPHALITIS.

Name, sex, age, date.	N. II.	Nerve III.				Photo- phobia.	IV and V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.
		Ptosis.	Diplopia	Light and accommodation.	Pupil.									
1.—U. H. (M.), 55 years Feb. 3, 1920	0	Bilateral	plus	Inability to read	Left dilated	plus	Pain; tremor in face 0	0	Lt.	Lt.	0	Pulse, 100	0	Lt.
2.—F. P. K. (M.), Edema 40 years Feb. 4, 1920		0	plus	....	....	plus		plus rt.	0	0	0	80	0	0
3.—F. S. B. (M.), 56 years Jan. 8, 1920	0	0	plus	....	....	plus	Pain in face	plus rt.	0	Rt.	0	...	0	0
4.—M. H. (F.), 20 years Jan. 23, 1920	0	Rt.	0	....	....	plus	Pain in face	0	Rt.	0	0	90	0	0
5.—O. S. H. (M.), Edema 50 years Feb. 27, 1920	left 0	0	plus	....	....	0	0	plus lt.	0	0	0	76	0	0
6.—J. D. (M.), 50 years Oct. 19, 1919	0	Rt.	plus	Absent	....	0	0	plus rt.	Rt.	0	0	90	0	Lt.
7.—J. S. (F.), 5 years May 23, 1919	0	0	0	....	Right dilated irregular Middilatation	plus	0	0	0	0	0	150	0	0
8.—H. H. (M.), 44 years Apr. 3, 1919	0	0	0	....	Sluggish	0	0	0	0	0	0	72	0	0
9.—J. C. (M.), 55 years Aug. 20, 1919	0	0	0	....	Middilatation	plus	0	0	0	0	0	90	0	0
10.—H. W. (M.), 46 years Feb. 17, 1920	0	0	0	....	Middilatation	plus	0	0	0	0	0	60	0	0
11.—E. L. C. (M.), 18 years Jan. 27, 1920	0	0	0	....	....	0	...	0	Rt.?	0	0	...	0	0
12.—Mrs. B. (F.), 45 years Feb. 2, 1920	0	0	0	No accommodation	....	plus	0	plus rt.	0	0	0	...	0	0
13.—M. M. (M.), 34 years Apr. 1, 1919	0	Rt.	plus	No accommodation	....	plus	0	plus	0	0	0	...	0	0
14.—I. Feb. 1, 1920	0	Rt.	plus	No accommodation	....	plus	0	0	Rt.	0	0	...	0	0
15.—G. V. (M.), 25 years Jan. 25, 1920	0	Lt.	plus	....	Both dilated	0	0	0		0	0	...	0	0

*Headache* appeared as an initial symptom in 12 cases and was present in 54 cases. It must have been confused in many instances with sensory fifth nerve involvement. Sore scalp was a common complaint. Hyperesthesias and anesthetics have been occasionally described. Severe toxic headaches occur at the onset and rapidly disappear as lethargy supervenes, unless meningeal involvement is present. Headaches in the early stages may be due in some instances to ocular disturbances, such as diplopia, photophobia, etc.

*Rigidity of the neck*, if present, is not, as a rule, marked. Confusion may be easily avoided in regard to this symptom if one remembers that increased muscle tonus is commonly a part of the picture of epidemic encephalitis. If marked rigidity of the neck, with Kernig's or Brudzinski's signs, exist, meningitis is to be looked for.

*Tremor* was present in 35 cases. The descriptions given are usually vague and inaccurate. The tremor is most commonly coarse, often unilateral and not intentional. Tremor, or twitching of the abdominal muscles, has occasionally been reported in the literature (Reilly<sup>18</sup> and Bassoe, *loc. cit.*). We have seen this symptom in 2 cases. Facial twitching preceding a facial paralysis by several days was noted twice in our series.

*Disturbances in reflexes* are not common or uniform. Four cases in the series showed an absence of deep reflexes or a hyporeflexia, 2 of which cases were fatal. The knee-jerks were as often increased as absent. Babinski's sign was present only 18 times and usually transitory. Oppenheim's sign was present in 5 of our 15 cases. Ankle clonus was present in 8 of the 115 cases. In 31 cases some changes in reflexes were noted. It would seem that the greatest value of a change in reflexes was to exclude functional disease of the nervous system, which may be difficult at the first examination. *Peripheral pain* is a common symptom, 26 cases out of the 115. It has not received the attention that it should, for we found it in 6 out of our 15 cases. The pain is commonly described as cramp-like, burning, boring, shooting, occasionally associated with paresthesia, and is of the neuritic type. We are convinced that it will be frequently found if inquired into. It is probably of meningitic, radicular or neuritic origin. If cases of present-day obscure pain, neuritic in character, are carefully investigated we feel sure that some of them will fall into the class of mild cases of epidemic encephalitis.

*Perspiration*. Sweating, judging from our cases, is very common, from the literature, very rare. Though present in all of our cases it was reported only 6 times in the 100 cases from the literature. In 6 of our cases it took the form of night-sweats, which were a

<sup>18</sup> Hitherto Undescribed Signs in Diagnosis of Lethargic Encephalitis, Jour. Am. Med. Assn., 1920, lxxiv, 735.

source of anxiety to the patient or to relatives. According to Crookshank (*loc. cit.*) "the sweating sickness" which was prevalent in England in the seventeenth and eighteenth centuries is the same disease which is now prevalent as epidemic encephalitis.

*Fever.* The average maximum temperature was 102° F. except in lethal cases, in which a prelethal rise to 105° or 106° was common. Complete absence of fever was noted in 50 of the cases. In all events fever was usually transitory and prevailed only for short periods of the disease.

*Laboratory Findings.* Leukocyte counts were reported on 36 of the 100 cases. They averaged 10,200 white cells, 72 per cent. of which were polynuclears. The highest count was 22,000. Of 25 counts in our series of 15 cases the average leukocyte count was 10,200, of which 71 per cent. were polynuclears. The red counts and the hemoglobin percentages were approximately normal. The Wassermann test was uniformly negative. Blood cultures were negative except in one case of the 15 series, from which a green streptococcus, which was agglutinated by the patient's serum, was isolated. The urine examinations showed only the usual changes encountered in acute infections.

TABLE IV.—CEREBROSPINAL FLUIDS.

Name.	Day of disease.	Appearance.	Pressure.	Cells.	Globulin.	Wassermann.	Gold chloride.
11.—E. L. C. . . .	18	Clear	plus 1	2 m.	0	0	112321000
11.—E. L. C. . . .	38	Clear	plus 1	2 m.	0	0	
11.—E. L. C. . . .	60	Clear	0	2 m.	0	0	122210000
10.—H. W. . . . .	30	Clear	plus 1	3	0	0	
9.—J. C. . . . .	90	Clear	0	0	0	0	
8.—H. H. . . . .	35	Clear	plus 1	16 m.	..	0	
8.—H. H. . . . .	41	Clear	plus 1	12 m.	..	0	
7.—J. S. . . . .	50	Clear	0	0	0	0	1355542000
6.—J. D. . . . .	10	Clear	plus 2	3 m.	0	0	
4.—M. H. . . . .	15	Clear	plus 1	3 m.	0	0	0122300
1.—U. H. . . . .	35	Clear	plus 2	24 m.	plus 2	0	12220000
1.—U. H. . . . .	49	Clear	plus 1	11 m.	0	0	112211000
1.—U. H. . . . .	63	Clear	plus 1	3 m.	0	0	1222110000
3.—F. S. B. . . .	70	Clear	plus 1	13 m.	0	0	00011111000
2.—F. P. K. . . .	70	Clear	plus 1	3	plus 1	0	1111100000
13.—M. M., S. Dak.	..	Clear	plus 1	..	plus 1	0	
14.—Iowa . . . .							
12.—Mrs. B. . . .	21	Clear	plus 1	3	0	0	
15.—G. I. . . . .	35	Clear	plus 1	0	plus 1	0	0122211234

*Spinal Fluids.* This table gives the findings in nineteen spinal fluids obtained from the personal series of 15 cases (Table IV). The average day of disease on which the taps were made was the thirty-sixth. The earliest tap was made on the tenth day and the latest on the ninetieth day. The fluids were all clear and came with increased pressure in 7 instances. The average number of



cells was 9 per cubic millimeter. The highest cell count was 24. The cells were chiefly mononuclears. Globulin (Nonne-Apelt test) was increased in 4 cases. All the Wassermann tests were negative. The gold chloride was mildly luetic in 7 out of 11 examinations in which this test was made.

In Table V are 64 spinal fluid examinations collected from the 100 cases in the literature. The average number of cells in the series was 16 mononuclears per cubic millimeter. The pressure was increased in only 10 per cent. The globulin test was positive in over 50 per cent.

**Pathology.** In a region so difficult to examine as the brain-stem it is remarkable how definite a pathological picture has been set forth by the investigators. Marinesco, McIntosh, Tilney and Riley and Bassoe have given us the most information. In the only case in our series which came to autopsy the congestion of the frontal lobes, the patchy edematous meninges and the marked thickening of the basilar meninges were apparent in the gross. On macroscopic sections the brain-stem substance was soft and numerous punctate hemorrhages were found in the mesencephalic and thalamic areas. Microscopic sections showed marked edema of the peri-aqueductal gray matter, with small hemorrhages into the white and gray matter. The venules showed perivascular infiltration, with lymphocytes, plasma cells and mononuclears. Many of the vessels were thrombosed. Neither neuronophagia nor satellitosis were present. The chief pathological changes as shown in the literature may be summed up as follows: (1) Meningeal edema and thickening; (2) softening and congestion of both gray and white matter of the brain and pituitary gland; (3) punctate hemorrhages in mesencephalon and thalamus and basal ganglia; (4) thrombosis of small vessels; (5) perivascular infiltration of small vessels of the brain-stem; (6) edema of the mesencephalic area.

**Prognosis.** Out of Barker's 8 cases none died; 6 of von Economo's 11 died; 7 of Netter's 15 cases died; 2 of Wilson's 13 cases died; 5 of Tilney's 20 cases died; 31 of the 100 cases collected from the American literature died. Of our series 4 out of 15 died, 4 recovered wholly in one and a half to four months and 7 at the end of two or three months had fifth, sixth, seventh and eighth nerve disturbances; one still had pain in the arm after two months. Disturbances in cerebration and equilibrium took on the average three or four months to clear up entirely. Facial nerve palsies lasted four or five months. Asthenia, depression and dizziness persisted seven months as an average. The fatal cases generally terminated in the first few days or weeks of the disease, so that the longer the course of the case the better the chances of recovery. The four deaths in our series resulted in three, five, six and sixteen weeks respectively.

TABLE V.—CEREBROSPINAL FLUIDS, 100 CASES.

	Appearance.	Pressure.	Cells.	Globulin.	Wassermann.	Gold chloride.
1 . . .	...	...	30 m.	plus 4	0	Luetic curve.
2 . . .	Clear	...	11 m.	plus 4	0	
3 . . .	Clear	...	133 m.	plus 4	0	
4 . . .	Clear	...	30 m.	plus 1	0	
5 . . .	Clear	...	2 to 7 l.	plus 1	0	Paretic curve.
6 . . .	Clear	plus 1	48 m.	plus 3	0	
7 . . .	Clear	plus 1	6 l.	0	0	
8 . . .	Clear	...	...	...	0	
9 . . .	Clear	...	...	...	0	
10 . . .	Clear	...	0	0	0	
11 . . .	Bloody	...	23 l.	0	0	
12 . . .	Clear	...	3 l.	0	0	
13 . . .	Clear	...	7 l.	0	0	
14 . . .	Clear	...	0 l.	0	0	
15 . . .	Clear	...	0	0	0	
16 . . .	Clear	plus 2	0	0	0	
17 . . .	Clear	...	4 l.	0	0	23433321100
18 . . .	Clear	...	85 l.	0	0	
19 . . .	Clear	...	20 l.	0	0	
20 . . .	Clear	...	64 l.	0	0	
21 . . .	Clear	...	66 l.	0	0	1221110000
22 . . .	Clear	...	7 l.	0	0	
23 . . .	Clear	...	29 l.	0	0	
24 . . .	Clear	...	4 l.	plus	0	
25 . . .	Clear	...	7 l.	0	0	0112111000
26 . . .	Clear	...	9 l.	plus	0	
27 . . .	Clear	plus 1	26 l.	plus	0	
28 . . .	Clear	...	25 l.	plus	0	
29 . . .	Clear	...	...	0	0	0122110000
30 . . .	Clear	...	4 l.	plus	0	
31 . . .	Clear	...	9 l.	plus	0	
32 . . .	Clear	...	10 l.	plus	0	
33 . . .	Clear	...	5 l.	0	0	1222110000
34 . . .	Clear	plus 1	12 l.	0	0	
35 . . .	Clear	...	...	0	0	
36 . . .	Clear	plus 1	35 l.	plus 1	0	
37 . . .	Clear	...	...	...	0	
38 . . .	Clear	plus 1	...	0	0	
39 . . .	Clear	plus 1	...	plus 2	0	
40 . . .	Clear	plus 1	1 l.	0	0	
41 . . .	Clear	plus 1	25 l.	plus 2	0	
42 . . .	Clear	...	150 l.	0	0	
43 . . .	Clear	...	150 l.	0	0	
44 . . .	Clear	...	50 l.	0	0	
45 . . .	Clear	...	40 l.	0	0	
46 . . .	Clear	...	30 l.	0	0	
47 . . .	Clear	...	29 l.	0	0	
48 . . .	Clear	...	106 l.	0	0	
49 . . .	Clear	...	110 l.	0	0	
50 . . .	Clear	...	60 l.	0	0	
51 . . .	0	...	5 l.	plus 1	0	
52 . . .	Clear	...	...	0	0	
53 . . .	Clear	...	...	0	0	2343341100
54 . . .	Clear	...	...	0	0	
55 . . .	Clear	...	...	0	0	
56 . . .	Clear	...	4 l.	0	0	
57 . . .	Clear	...	9 l.	0	0	
58 . . .	Clear	plus 1	...	plus	0	
59 . . .	Clear	plus 1	60 l.	plus	0	
60 . . .	Clear	plus	26 l.	0	0	

**Treatment.** There is no specific treatment. Adequate nursing, absolute rest and freedom from all excitement is imperative. Hospitalization is to be advised because of better control of laboratory facilities and of the desirability of repeated lumbar puncture. Lumbar puncture was of decided benefit in 10 of our own cases. The patients were brighter, the cranial nerve palsies were improved and headache was often relieved. Opium should be used with care except in the early states, when the pain is severe. The eyes must be protected from the light and from foreign bodies in cases of corneal anesthesia and orbicularis paralyses. Large doses of urotropin have been advised, but there would seem to be little evidence in favor of its use. The fluid intake of the patient should be maintained at a high level. The skin demands attention, as bed-sores are common.

**Conclusion.** It was thought that a statistical tabulation of the symptoms and findings of epidemic encephalitis as revealed in the American literature might be useful, especially in the recognition of the mild or aberrant forms of the disease, which would seem more numerous than is generally appreciated. A basis for the evaluation of symptoms is necessary in a disease the diagnosis of which must be made by exclusion. Either cranial nerve involvement (especially eye muscle disturbances), with or without lethargy or lethargy alone, constitutes sufficient grounds for a diagnosis of epidemic encephalitis in the presence of an epidemic when either is supported by a normal spinal fluid or an atypical spinal fluid in which there is a slight increase in cells or in globulin, or in both, a negative Wassermann, a mild paretic or luetic gold chloride curve and negative bacteriological findings.

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## A CONSIDERATION OF THE AFTER-CARE OF ARRESTED CASES OF ESSENTIAL EPILEPSY.<sup>1</sup>

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SEVERAL years ago I reported a series of arrested or cured cases of essential epilepsies before this Society.<sup>2</sup> The period of arrest

<sup>1</sup> Read before the American Neurological Association, June, 1920.

<sup>2</sup> The Curability of Idiopathic Epilepsy, with a Report of Twenty-nine Cures, Arch. Int. Med., January, 1912.

extended from four to twenty years. I desire at this time to make a few practical comments upon these old cases and add a few notes upon some others, and thus give a proper estimate of the prognostic permanency of an arrest and also to emphasize the importance of a follow-up treatment in all so-called cured cases. There can be little doubt that at least half of the relapses, after apparently more or less enduring arrest, could be prevented by the continued oversight and direction of the after-life of the discharged patient. This principle would not be so difficult to follow were the patients and relatives frankly dealt with regarding the proper mental hygiene which should be employed. The physician's attitude in this respect should not be dissimilar to that assumed in handling tuberculous cases whose active disease process has been brought to an arrest. It may be remembered in my previous report of some thirty cases it was a rather remarkable fact that fully two-thirds of the number reported had a more or less bad heredity. In spite of this handicap none of these cases has relapsed. Neurologists look askance at a good prognosis in such epileptic individuals, yet here another theoretical and tragic view is killed by a fact. Further, neither the length of time the disease had been existent nor the general nature and frequency of attacks played a conspicuous role in estimating beforehand the curable from the incurable. In a review of this entire material one obvious fact, however, not heretofore taken into precise account, was that all the arrested cases did not possess a marked predisposition in makeup, and that soon after coming under a precise training treatment their disease became modifiable by hygienic methods. In none of my arrested cases, as well as those of the literature on the subject, no mere one organ disfunction could have explained the epilepsy or its arrest. The disharmony of the organism as a psychobiologic whole was the great fault, and striving to overcome these special defects while modifying the general life of the individual epileptic was really what brought about a successful arrest.

These general principles are to remedy the innate defects of the constitutional makeup of the epileptic or to so adjust his life that he may find a non-stressful adjustment proportionate to his capacity of adaptation. We are all aware that, as a rule, the epileptic as an individual is incapable of the normal stress life, and even though he ceases to have fits, his epileptic makeup may still be manifested in untranquil moods, states of extreme sensitiveness, anger, petulance and sullenness, so that these less-pronounced epileptic reactions must approximate the normal before we can entertain hopes for any permanency of an arrest of the disease. One invariably finds these slighter indications of the great disorder, which formerly loomed large in the former patient's life, before actual fits recur. These temperamental faults are often not self-generated, but may

be a stress reinvented by the parents and relatives who, having held themselves in check and being also somewhat similarly temperamentally endowed as the patient himself, may begin to apply too quickly and severely a disciplinary life to the former epileptic patient. A severe type of stressful life is not and can never be thoroughly met. The patient makes a struggle to meet the new demands, but sooner or later succumbs. In searching for the cause one should remember that the physical and mental stress factor is most frequently not immediate to the attack but may be days or weeks precedent to the actual breakdown in seizures.

Two cases of recurrence of attacks after a free interval of years will be briefly cited to illustrate the careful oversight the more permanently arrested cases need if they are to remain free from fits. A clinical study of the cases has been previously reported.<sup>3</sup>

CASE I is now a boy of eighteen years, an only child, born of epileptogenic stock, whose epilepsy developed at eight years. Our patient walked at eighteen months and began talking rather late at two years. He was a crying, difficult baby. He entered public school at seven but did poorly there, being inordinately slow and inattentive, and at the end of two years he was removed on account of "anemia and nervousness." At ten he attended private school, but nervousness and attacks caused his removal.

The first epileptic attack came on after a period of prolonged mental stress in keeping up with his English classes. One morning, while hurrying to get off to catch a train, he complained of dizziness and immediately fell into a severe grand mal attack. Attacks followed this first one at fairly regular intervals of every two or three months until January, 1914, after which he had no attacks for two years. After eighteen months of training treatment, and in the absence of any seizure phenomena, it was decided to allow him to return to public school, which was done for a full-time attendance without the physician's knowledge. He went back to the full-time work with the old dislike, although he was only six months behind the grade of his age. Things would have gone fairly well, perhaps, if he had had some special tutoring or a little more consideration from the teachers, who, it must be said, are often prone to be merciless upon a backward pupil. He was still poor in English and mathematics, and although he would like to have engaged in sports after school, the extra time required for his studies gave him little opportunity. The lack of a full amount of time to play, once not cared for, now became very annoying, and it was often difficult to get him to his meals when out playing. The school work gradually grew more severe; in addition to English and mathematics, in which he stood poorly, he strove to gain a standing in geography, which would enable him to enter the final examinations. An attack finally

<sup>3</sup> Clinical Studies in Epilepsy, Psychiat. Bull., January, 1916-January, 1917.

occurred on December 26, 1915. The school life was again readjusted and there was another long, free interval from attacks (four years).

We have in this boy the makeup in which seizure reactions were induced by a too stressful demand at school. When he was withdrawn from this difficulty and placed in an ideal environment, with a chance to develop spontaneous interests, he became responsive and began to adapt himself fully to a proper physical and mental adolescence. But when he was again thrown into the same difficulties he broke down as he did at first. After having passed a period of four years of arrest he had an attack in December, 1919, which seemed to have been stupidly brought about by the mother's insistence that her only son go to college. To do this he once more went back into the close confinement of a preparatory school in a neighboring city, took up languages and all the studies, at which he did poorly and consequently hated. He stood the application and restraint without protest, but did his work worse and worse, his reaction time increased, he dawdled more and on being pulled up sharply the renewed tension once more broke him into frank epileptic attacks. Often it seems impossible for parents to learn the innate limits of physical and mental capacity in their epileptic children; hence the importance of keeping these arrested cases under medical supervision. This boy is now again doing nicely in an all-year-round training camp; he is no longer required to look forward to a college career, but is taking a practical concrete engineering course.

CASE II is a boy of fourteen years of age whose grand mal epilepsy was in arrest for seven years. He had attacks usually in a series of two to ten, and had at least three or four status periods, in one of which he had 150 grand attacks in a single day. There was no distinct nervous disorder in the family stock, but many of the father's relatives possessed the epileptic character. Our patient was a crying, stubborn child. He attended school for three months, his first trial at five years of age. It was not only difficult for him to apply himself while there, but he was absolutely incorrigible and could not sit still in the classroom. He was very sensitive, and when reprimanded often cried himself to sleep even after the mildest chastisement. He never played any game in which he could not be the leader. While it was possible for him to endure the demands of home life with rages and tantrums, later when these had to be repressed at school he could not subordinate his crude individualistic tendencies. First he grew listless, then more irritable and finally broke into an uncontrollable temper, was punished and sent home. His first grand mal attack came on one night after a particularly exasperating day at school, but he had been steadily growing more irritable and run down for a month before. After the first attack he still continued at school, with all its steadily accumulating



annoyances, until a month later, when he had five grand mal attacks in one night; since that time he has not gone to school. He was allowed to do just as he pleased, to go and come with his father in the fishing boats as he liked. In a few weeks the attacks began to subside, but he still was very irritable; little or nothing seemed to precipitate tantrums and rages, but the latter were not so severe or prolonged. Under training treatment and directing his interests from the abstract work at school to a concrete outdoor life, he gradually became more tranquil and quiet and the attacks ceased.

We now have this boy after an arrest of seven years from his disease once more becoming epileptic. We find the mother anxiously pushing him in the ordinary abstract training at school. He has had three convulsions, the first occurring in November, 1918, the second a year later, and the third in March of this year (1920). There are days when he feels stupid and can do nothing correctly; the parents have learned to put absolutely no duties upon him on those days, either in school or at home: he complains of his head feeling bad and can hardly recall anything that might have transpired during that period, showing a state of acute exhaustion due to forced efforts at school work. In each case it was one of the "dopey" days when the convulsion occurred. These days are from two to four weeks apart, usually caused by some extra excitement or fatigue. He is now five feet ten in height and weighs 143 pounds. He attends public school, and while he is behind most children of his age, he has been promoted each year. He enjoys arithmetic the best of his studies but the past year has become more interested in reading. He is very much interested in anything of a mechanical nature, especially electricity, wireless operating and automobile repairing. During the summer he works for his father around the water and in the fish market, is on regular wages and works very well, but must be watched carefully to see that he does not overdo.

As in Case I, family pride and stupidity seem to be equally responsible here. Parents of epileptic children must learn that even though free from seizures they are capable of withstanding only a certain amount of stress. If they cannot learn this then physicians must continue medical oversight.

Our next case has been in arrest for six years without any relapses to the present time.

CASE III is that of a boy, aged nineteen years, who had petit mal attacks, which he termed "dreamy turns," at eight years of age. He was born of fairly healthy stock. He had no other physical disorder aside from the petit mal and never had any grand attacks. The petit mal occurred as frequently as twenty to thirty a day. He was going to school at the time he came under my care, a few months after the petit mal began. He got along fairly well at school and did not feel particularly fatigued, although he was restless and nervous. He was always quick and impulsive in temperament and

lively and active at play. He was not a difficult child and took discipline well, although very sensitive. The bromide administration was discontinued, he was placed on a diet and a normal living regimen was established. The dreamy turns gradually became more infrequent, until by twelve years of age they had entirely ceased. He continued his education, went to a boarding academy and made satisfactory progress. He finished his schooling at sixteen and entered an exporting firm, which position he has been in for the past three years. He experiences no sensations at all, and states he can stand all sorts of stress. He eats and sleeps well and rarely gets rushed or fatigued. He is at the present time a tall, well-proportioned youth, and is the picture of health.

In this instance it was possible by tranquillizing the home environment, teaching a mild but consistently regular discipline and the induction of the proper physical regimen to restore this patient to a state of normal health. His present work enables him to gradually increase his hours of responsibility proportionate to that which he is able and desirous of undertaking.

CASE IV.—Our next case is a man of twenty-two years, whose epilepsy has been in arrest for three years. He was born of neurotic parents. At birth he showed an extraordinary supersensitiveness—he started, trembled and cried at the least excitement. His first attack occurred at five years after physical exhaustion and eating indigestible foods, since which time he has had attacks on an average of one or two each year. He learned easily, but his interest in school was so dilatory that his standing was poor. He was so supersensitive that “bad news always made him sick.” It would be days before he could get over disappointments. He was very affectionate, conscientious and overprecise about everything, and has always been so from earliest childhood. Four years ago this patient spent several months at Craig Colony, where he kept actively employed, with various mechanical occupations, repairing automobiles, etc. As an illustration of maladjustment the following psychotic episode is so classic as a forerunner to epileptic attacks that this patient’s statement may be given here to show his attitude toward his environment:

“Two months ago I noticed that I was getting irritable and dissatisfied. It was difficult to get used to the life here, but I tried hard. I felt suppressed on account of the restrictions, and the daily routine was so trying, but the doctor said it was the right place for me, so I made up my mind I would stay or die. Gradually the feeling became so strong I felt I must get away. I could not bear it any longer. I missed the social life—no dancing or anything. The feeling kept getting worse. If I even spoke to a girl I was reported. One evening another fellow and myself took a walk with two girls and next day I was severely reprimanded. I cannot tell you how I felt that night. I cannot recall any dreams. I thought

that if I could not even take a walk without being called down that I would go home or some place else where I would have some rights. Things kept getting worse, and I thought more and more of home and began to write telling how dissatisfied I was with everything. When I get thinking about home and about writing home I always feel depressed, and I am not satisfied until the letter is written. When I had finished a letter to my mother I went to post it and had the attack on the way. I felt tired afterward and did not feel like doing anything. I had been looking forward to having a vacation, but the attack seemed to take the desire away and I began to feel I was not able, and the doctor would say it was foolish to think of going away. So the wanting to go did not seem so strong. After the attack I think I was relieved a little of the extreme irritation—for a time at least. I feel sure, however, that this attack would not have come on if I had had a vacation at the time I wanted it."

After leaving the Colony our patient worked in a garage repairing automobiles, and although he worked hard he seemed to feel quite content to do so. In the fall of 1918 he went to a training camp as a Y. M. C. A. Secretary and stayed there until August, 1919. He then took up salesmanship in a motor car company and continues in this field. He is out in the open air a great deal, is interested in his work and feels that he has entirely recovered from his epilepsy. He has been free from attacks for over three years.

One often hears the inquiry, Do epileptics themselves really gain an insight into the nature of their disorder and their innate temperament? A propos of this I may extract a paragraph from this former patient's letter:

"I always look back with gratitude to the time my eyes were really opened to the nature of my disease and the kind of individual that I am. In addition to paying proper attention to the routine of living I keep myself properly and interestingly employed. I take no sedatives or laxatives, and am in good physical trim. I know full well that my victory over my disease has been brought about by my learning about myself. I suppose I shall always have to refrain from certain stresses and things of an irritating nature."

Unfortunately not merely insight but reëducation is necessary before an epileptic individual may be permanently helped. This latter case underwent a training treatment of three years before the desired results were obtained.

CASE V.—The final case may be briefly cited of a man, now thirty-five years old, who has been free from grand mal attacks for over ten years. The grandfather and father were both epileptic. Our patient had been for ten years an epileptic, when a general training plan of treatment was undertaken. He is a college-trained agriculturalist and now owns and operates a large grain and fruit farm. He was married several years ago after a vasectomy. In the absence

of a family of his own he has adopted several children and is living a contented and happy life. He is so sure of his poise and tranquillity of mind that he contemplates having the function of the vasectomy restored, but the possibility of the transmissibility of so strong a heredity is a factor which must be given serious consideration.

We may conclude that: (1) So-called cures or arrests in essential epilepsies are brought about only by the most thorough-going and prolonged plan of neurologic and hygienic training treatment in which reëducation is the basic factor. (2) That relapses in arrested cases occur through negligence or disregard of the essential factors. There is renewed and intensive physical and mental stress and that proper and appropriate medical supervision should be continued throughout the lives of such individuals. Such a plan of after-care in private and institutional practice would greatly diminish the possibilities of relapses. (3) That a more or less enduring arrest and cure in essential epilepsy may be considered permanent when the environment and life reactions as regards the secondary epileptic reactions are approximately normal. That no mere cessation of epileptic fits under sedatives should be held out as an enduring arrest unless the individual shows a corresponding absence of epileptic reactions of all sorts.

## VIRULENT DIPHTHERIA BACILLI CARRIED BY CATS.<sup>1</sup>

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THE available literature dealing with the transmission of diphtheria from cats to human beings is not convincing, due chiefly to the fact that the bacteriologic studies and reports are incomplete. However, many instances are on record which apparently show a relationship between animal and human infections, based upon clinical observations alone.

Thirty years ago Klein<sup>2</sup> described lesions in cats which he considered typical of natural infections with diphtheria bacilli. Low,<sup>3</sup> in 1888, reported the occurrence of four cases of diphtheria in one house, which he thought had been carried by a pet cat from another case in the same neighborhood. Cultures from this cat contained

<sup>1</sup> Published with permission of the Surgeon-General, U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

<sup>2</sup> Local Government Board Report (Gr. B.), 1889, pp. 162-174.

<sup>3</sup> *Ibid.*, 1888, xviii, 131.

morphologically typical diphtheria bacilli. Karlinski,<sup>4</sup> in 1908, published observations of an outbreak of diphtheria which resulted in the death of seventeen out of twenty-four Angora cats. He stated that typical pseudomembranous lesions were found from which he isolated virulent Klebs-Loeffler bacilli. He also reported a number of cases of diphtheria in children who were infected after contact with sick cats. In the same year Graham-Smith<sup>5</sup> made the following statement: "A general impression prevails that cats contract diphtheria from human subjects and very numerous instances are quoted in the literature of cats apparently suffering from diphtheria communicating it to children; and other examples are quoted of cats, although remaining quite well, being the only probable carriers of infection. Very few of these cases seem to have been bacteriologically examined, and in no instance has the presence of diphtheria bacilli been satisfactorily proved."

The following case was brought to my attention in July, 1919, by Capt. W. C. Deming, M.C., U.S.A.:

Mrs. P., an elderly lady, who lived in Maryland, had been very ill with a "severe tonsillitis" for four days, when Capt. D. was asked to see her on July 13, 1919. Examination at that time showed that the patient's uvula, both tonsils and posterior pharynx were covered with a grayish-brown false membrane. She breathed with difficulty and appeared to be very weak. Ten thousand units of diphtheria antitoxin were given immediately and cultures were made from the pseudomembrane. In spite of treatment the patient died early the following morning. The culture, which was examined at the Walter Reed General Hospital laboratory, showed a luxuriant growth of diphtheria bacilli. These organisms killed guinea-pigs in six days after subcutaneous injection, but failed to produce lesions in animals previously injected intraperitoneally with diphtheria antitoxin.

*Cat A.* A pet cat, which often slept in the bed with Mrs. P. and was "constantly fondled by her," had been sick one week before the patient's illness began. The cat had a "croupy cough, was unable to swallow food, became very thin and cried continually." It was thought that a piece of chicken bone had become lodged in the animal's throat. The cough persisted until July 13, after which the cat appeared to be improving, although it was still quite thin. Throat cultures on July 14 showed bacilli which were morphologically similar to those obtained from the patient. The virulence for guinea-pigs of the two cultures was also the same. Two days later the cat was chloroformed and a careful postmortem examination was made. The only lesion found was a small oval

<sup>4</sup> Ueber eine durch Hauskatzen Verbreitete Diphtheritis-epidemie bei Kindern Heilkunde, Berlin. u. Leipzig, 1908, p. 129.

<sup>5</sup> The Bacteriology of Diphtheria (Nuttall and Graham-Smith), Chapter VII, p. 281.

ulceration covered with a yellowish-gray pseudomembrane, between two smaller red inflammatory areas on the upper surface of the left nasal fossa (Fig. 1). Neither the fatty degeneration of the kidneys described by Klein nor any other lesion of the internal organs was found. Cultures made from the nasal pseudomembranous lesion contained diphtheria bacilli.

*Cat B.* Throat cultures made of another cat which had often played with Cat A were positive July 18 for morphologically typical diphtheria bacilli. After confinement in a cage at the laboratory



FIG. 1.—Nasal diphtheria. Cat A (specimen in Army Medical Museum, Washington, D. C.). The lower jaw has been removed and an opening made through the roof of the mouth into the nasal fossa. Virulent diphtheria bacilli were isolated from the small oval lesion on the left.

for eight days this cat died. At necropsy small, elongated, grayish-white patches of pseudomembrane were found covering ulcerations of the vocal cords. These were surrounded by a narrow red area (Fig. 2). Diphtheria bacilli, which killed guinea-pigs in four days, were isolated from these lesions. Diphtheria antitoxin protected guinea-pigs against this organism.

Three stray cats caught on the hospital grounds and examined at this time were negative. A small, slender, granular, Gram-positive bacillus of the diphtheria group was obtained from the

throat of Cat 1. However, it differed culturally from the true diphtheria bacillus and was not virulent for guinea-pigs. None of the control cats showed any pathologic lesion.

**Bacteriologic Data.** The organisms isolated from lesions of cats A and B and the patient, Mrs. P., showed the following common characteristics: Colonies were grayish-white, moist, confluent and non-adhesive after growing upon Loeffler's serum media at a temperature of  $37.5^{\circ}\text{C}$ . for twenty hours. After several days' incubation they became yellowish. There was no proteolytic action in cultures six weeks old. Granular bacilli similar to Wesbrook's types C and D, which were Gram-positive, Neisser-positive and not acid-

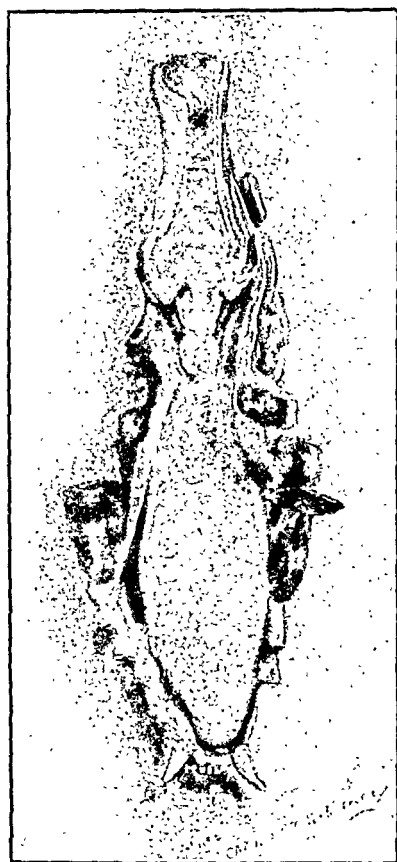


FIG. 2.—Laryngeal diphtheria. Cat B (specimen in Army Medical Museum Washington, D. C.) shows lower jaw, upper portion of the trachea and the larynx spread open. Virulent diphtheria bacilli were isolated from ulcerations on both vocal cords.

fast predominated in smears from the younger colonies. In glucose infusion broth cultures a granular deposit was formed without clouding. Pellicle formation occurred. Small, round, moist, gray, non-hemolytic colonies were formed on horse-blood agar plates in twenty-four hours. A trace of acid without coagulation developed

in litmus milk cultures. No indol was formed. Acid without gas was formed in glucose, maltose and dextrin; alkali in mannite and inulin, while no change in reaction occurred in lactose, xylose and arabinose broth cultures. Both cat cultures produced acid in saccharose while the patient's culture became alkaline. As the ability of diphtheria bacilli to ferment saccharose is extremely variable, this difference does not prove that the three strains were unrelated. For the determination of virulence, guinea-pigs weighing 300 grams each were inoculated subcutaneously with 1.5 c.c. of seventy-two hour broth cultures, and animals were examined as soon after death as possible. A similar dose was given to control guinea-pigs previously inoculated intraperitoneally with 100 units of diphtheria antitoxin. None of these control animals died. Cultures from Mrs. P. and from Cat A both killed pigs in six days, while the Cat B culture killed a pig in four days.

Source of culture.	Granular bacilli.	Days required to kill guinea-pig.	Control guinea-pig (diphtheria antitoxin).	Typical reaction to stains.	Typical characteristics on Loeffler's media and broth.	Acid production—carbohydrate media.								
						Glucose.	Saccharose.	Maltose.	Dextrin.	Inulin.	Mannite.	Lactose.	Xylose.	Arabinose.
Cat A became ill July 2; lesion left nasal; partial recovery; chloroformed July 16	Yes	6	Lived	Yes	Yes	Yes	Yes	Yes	Yes	No	No	0	0	0
Patient, Mrs. P., became ill July 9; lesion pharyngeal; died July 13	Yes	6	Lived	Yes	Yes	Yes	No	Yes	Yes	No	No	0	0	0
Cat B became ill, date unknown; lesions of vocal cord; died July 26	Yes	4	Lived	Yes	Yes	Yes	Yes	Yes	Yes	No	No	0	0	0
Positive control (National Vaccine Co. strain)	Yes	1½	Lived	Yes	Yes	Yes	No	Yes	Yes	No	No	0	0	0
Cat No. 1; negative control from post	Yes	Avirulent		Yes	No	Yes	No	Yes	Yes	No	No	0	0	0
Cat No. 2	No organisms of the diphtheria group found.													
Cat No. 3	No organisms of the diphtheria group found.													

Yes = acid.

No = alkali.

0 = no change.

The organisms obtained from the throat culture of control Cat 1 was a small, slender, Gram-positive, non-acidfast granular bacillus. Colonies on coagulated serum media were yellowish, round, dry,



adherent and emulsified very poorly. No proteolytic action was observed. Cultures had a disagreeable odor. A cloudy growth without pellicle formation occurred in glucose infusion broth cultures. Colonies on horse-blood agar plates were gray and very minute even after forty-eight hours' growth. Litmus milk was unchanged; no indol was formed in peptone cultures. Acid was formed in glucose, maltose and dextrin; alkali in saccharose, inulin and mannite, while no reaction occurred in lactose, xylose and arabinose broth cultures. This organism was not virulent for guinea-pigs.

The history of contact and the dates of infection, when considered with the bacteriologic findings, suggest that Cat A was the source of the diphtheritic infection developed by Mrs. P. as well as that of Cat B, but this cannot be proved. However, it is certain that both of these cats were infected carriers of virulent diphtheria bacilli and therefore a menace to human beings.

**Summary.** 1. An elderly lady developed a fatal diphtheritic pharyngitis after close contact with a cat (A) which had been sick one week.

2. A second cat (B) which had been in contact with the first cat (A) became sick and died ten days later.

3. The patient had a grayish-brown pseudomembrane covering her uvula, tonsils and posterior pharynx. Cat A had a small yellowish-gray pseudomembranous ulceration in the left nasal passage and Cat B showed ulcerations of both vocal cords, covered with a grayish-white false membrane.

4. Diphtheria bacilli of intermediate virulence for guinea-pigs were isolated from all three lesions.

## REVIEWS

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PRACTICAL PHYSIOLOGY. By RUSSELL BURTON-OPITZ, M.D., PH.D., Associate Professor of Physiology, Columbia University, New York City. Pp. 238; 123 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

WITHIN a few months after the publication of his acceptable *Text-book on Physiology*, Burton-Opitz presents an equally acceptable volume on *Practical Physiology*. This manual consists of preface, fifty lessons occupying about three hours each, a list of fifty demonstrations (without directions—for use at the discretion of the demonstrator—and making a satisfactory supplement to the students' experiments), interleaves for special notes (students are expected to keep collateral note-books for verbal or kymographic records of results), tables of weights and measures with metric equivalents and complete index. Topics for experimentation cover basic subjects: First, physiology of muscle and nerve, then circulation, respiration, nervous system and sense organs, concluding with digestion, absorption and excretion. In general the apportionment is well balanced although nervous system and sense organs might well have a larger share. Illustrations are a notable feature consisting of diagrams of apparatus, arrangement of apparatus with tissue or organ, copies of kymographic records and anatomical areas. Directions are marked by conciseness and demand for only simple apparatus.

Many teachers of physiology will doubtless agree with the reviewer that this book would be of even greater value if arranged topically only; because inequality of work necessarily occurs. We hope that in his next edition Burton-Opitz will adopt this less mechanical plan.

In the preface the author explains the "inestimable value" of experimental physiology to students. "It cultivates the faculty of close observation and accurate rating of facts. It develops the power of logical thought and expression and impresses upon them facts and principles otherwise scarcely noted and comprehended. . . . It also enables the students to familiarize themselves with the use of operative instruments and the action of different drugs." Plainly, such training is the stepping stone to clinical medicine, therefore teachers and students of physiology are indebted to the

author for emphasizing this application of physiological principles which is an important line of progress today. This book deserves a place in the equipment of every physiological laboratory.

R. W. L.

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HERMAN'S DIFFICULT LABOR. By CARLTON OLDFIELD, M.D. (LOND.), F.R.C.S. (ENG.); Hon. Obstetric Surgeon to the General Infirmary, Leeds; Lecturer in Gynecology, University of Leeds; Hon. Medical Officer to the Maternity Hospital, Leeds. Sixth edition, revised and enlarged. Pp. 573; 198 illustrations. New York: William Wood & Co., 1920.

THE present edition of this standard text-book on obstetrics appears under the editorship of Dr. Carlton Oldfield, who has revised and enlarged the text of the fifth edition, which appeared in 1910. As the previous editions have been extensively reviewed in this JOURNAL, an exhaustive review seems unnecessary and attention will be called only to the principal points of the revision.

The influence of the progress in surgery made during the World War is reflected in the recommendation of the use of the Carrel-Dakin treatment in cases of incomplete rupture of the uterus and septic conditions of the pelvis. The section on Cesarean section has been rewritten and its more extended use advised in certain forms of antepartum hemorrhage. The subject of transfusion for hemorrhage and shock following delivery is especially well handled. The volume closes with chapters on retrodisplacement of the pregnant uterus and eclampsia, which while not examples of difficult labor are pertinently included in a book of this nature. The remarks on arterial pressure in pregnancy and eclampsia are not in accord with the teachings of most American texts on obstetrics.

P. F. W.

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THE PRINCIPLES OF ANTENATAL AND POSTNATAL CHILD PHYSIOLOGY, PURE AND APPLIED. By W. M. FELDMAN, M.B., B.S. (LOND.). Assistant Physician to and Lecturer on Child Physiology at the Infants' Hospital. Pp. 694; 129 illustrations and 6 plates. London, New York, Bombay, Calcutta and Madras: Longmans, Green & Co., 1920.

THIS rather unusual monograph aims at encompassing within a single volume a complete and detailed account of the up-to-date physiology of the various antenatal, natal and postnatal phases of child life, and the author has succeeded remarkably well in achieving his purpose. While the book is really a compilation of extracts from the literature on this subject, yet the assimilation of

the abstracts and the arrangement of the text makes the reading an easier matter than to be expected. The book will be of interest not only to the embryologist and physiologist from the aspect of the pure principles of development and organization of the fetus and child, but as well to the pediatricist and obstetrician from the practical application of these principles to the problems of the newborn and growing child. The natural discussion of the merging borders of pathologic and normal physiology of the various periods serves only to enhance the value of the book, and it should be a welcome reference volume to the classes of readers named.

The book is divided into four parts: Part I takes up the physiology of the anteconceptional and conceptional germinal stages, with an extended discussion of the laws of heredity and the post-conceptional or intra-uterine stage, the physiology of the developing child and the physiology of pregnancy. The chapters on fetal development and physiology comprise a full third of the text and form an exhaustive review of the literature of the past thirty years on this subject. Part II deals rather shortly with the physiology of birth. To the reviewer it seems that the scant paragraph on the effect of labor on the fetus might be lengthened to include a discussion of fetal asphyxia and some of the other forms of altered physiology which result in fetal death during birth. And while the spirit of criticism is present, it may be mentioned that in Part III the section on hemophilia is not fully covered at least in American literature. The postnatal stage, Part III, begins with the physiology of the neonatal period and thence progresses in an orderly manner through the various periods of infancy and childhood to puberty and adolescence, giving a history of the growth and development of the different body systems in their manifold physiologic changes. Part IV is an estimable *résumé* of the anatomic and physiologic peculiarities of the premature infant which merits more than passing attention. The text is interspersed with numerous illustrations, charts, tables and diagrams correlating the text and showing more clearly the application of the principles of physics and physical chemistry to the physiologic principles discussed.

P. F. W.

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RESEARCHES IN UROLOGY. COLLECTED REPRINTS FROM THE BRADY UROLOGIC INSTITUTE, Johns Hopkins University and Hospital, Baltimore. Volumes I and II, 1920.

THE reviewer was astonished, some years ago, to hear an enthusiastic novitiate in a specialty say that he had listed eighteen different problems for research investigation in his field that he felt would be interesting and productive. Doubting that any average specialist could write offhand a dozen such problems in his limited field of work, it is a real pleasure to find in these two

volumes, representing seven years' work, such a remarkable diversity of endeavor. There are 97 reprints representing 50 separate research studies, 22 articles dealing with interesting case reports and new operative procedures, and the remaining 25 are of general character, such as papers read before societies summarizing work along certain lines.

Volume I groups together papers on the kidney, the ureter and the bladder. Here will be found the collected reprints of Macht's work on the "pharmacology of the ureter," the effect of various poisons and alkaloids, leading up to the demonstration of the action of papaverin as the best inhibitor of smooth muscle spasm; Burns' work on thorium as an agent for pyelography; Geraghty on pyelitis, on bladder tumor, on primary hydronephrosis and on kidney function tests; Young on fulguration of incarcerated ureteral calculi, on his "punch" operation, on the surgical treatment of vesical diverticulæ, a valuable study on the embryology and surgery of double ureter and kidney, and a graphic description of the formation, building and operation of the Brady Institute.

Volume II groups together the papers on the prostate, the urethra and miscellaneous subjects. Again we find the pharmacological work of Macht, with the development of benzyl benzoate; White's, Davis's and Hinman's studies on urinary antiseptics, work that has produced at a later date mercurochrome; Young's researches with radium and surgery in prostatic carcinoma; Watson and Geraghty on the development and pathologic roles of the seminal vesicles; Hinman on testicular tumors; Young's new operation for epispadias and Young and Stone's operation for urethrorectal fistula.

There is no doubt that such centralization of interests is the ideal way to stimulate research. However, it is burdened at the same time with the artificial stimulus that production is essential. These volumes contain but little chaff and their greatest value lies in the grouping of allied papers otherwise scattered in the journal literature, in an appreciation of the splendid work being done for the advancement of knowledge, and in the incentive to new thoughts that their perusal gives. A word must be added to commend the excellent illustrations by Didiesch that many contain.

A. R.

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MANUAL OF PEDIATRICS. FOR STUDENTS AND DOCTORS. By DR. WALTER BIRK, Professor of Pediatrics, University of Tübingen. Volume I. Fourth edition. Pp. 269; 25 illustrations. Bonn: A. Marcus & E. Weber, 1920.

THE first volume is devoted to the diseases of infancy. The first chapter gives the physiology and pathology of nursing, and

is shorter than similar portions of American texts, but it furnishes the information in a concise form. The second chapter presents the physiology and pathology of the newborn in a brief but sufficiently detailed manner. The third chapter deals with the nutritional disturbances of infancy and their treatment. This forms the larger part of the volume and is excellent in the manner of presentation and in the information given. No space is devoted to the various methods of working out percentage formulæ. When mixtures are recommended they are given in terms of fractional quantities of the ingredients, as, for example, one-third whole milk and two-thirds barley water. A broader consideration of methods of infant-feeding in addition to the author's own would have greatly enhanced the value of the book as a work of reference. The final chapter outlines the other diseases of infancy. The chronic infections, such as tuberculosis and syphilis, diseases of the urinary, cardiac, respiratory and nervous systems are covered in a very sketchy manner. Here also the value of the book for reference purposes is greatly diminished by the condensation of these important subjects apparently to conform to a restricted size. It was a disappointment not to have found recorded some facts as to the nutritional and general disorders of infants incidental to four years of war diet and abnormal living conditions.

A. E. S.

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A DICTIONARY OF TREATMENT. By SIR WILLIAM WHITLA, M.A., M.D., LL.D., M.P. Late Professor of Materia Medica and Therapeutics in Queen's University, Belfast; Consulting Physician to Royal Victoria, Belfast Ophthalmic and the Ulster Hospitals for Women and Children. Sixth edition. Pp. 1083. Chicago Medical Book Co., 1920.

THE appearance of the sixth edition of this book, and the fact that this present edition brings the total number of these books printed up to 32,000, shows that the presentation of therapeutics in this form is decidedly popular. The treatment of every conceivable condition is given some space in the book whether the condition is orthopedic or surgical, or whether it belongs to the realm of the dermatologist or to the internal medical man. As evidence of a large and diverse number of subjects treated we might mention the first three and the last three subjects that are indexed. They are respectively: Abdomen (gunshot wounds of); abortion; abscess; and writers' cramp; yaws; yellow fever.

The dictionary is carefully and conscientiously prepared and satisfactorily abbreviated. Necessarily in the short space that is at his command the author can devote only a relatively brief paragraph to any given subject; for example under fractures, only

the general principles of treatment are given, a procedure which is eminently wise. The one disadvantage of the book to the American physician is the frequent mention of drugs or other preparations which are not in the American *Pharmacopeia*. It must not be forgotten also that the strength of some of the preparations differ in the British and American *Pharmacopeias*. J. H. M., JR.

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THE OXFORD MEDICINE ADVANCE PAGES. Edited by HENRY A. CHRISTIAN and SIR JAMES MACKENZIE. Volume I, Part V. Pp. 635; 23 illustrations. New York: Oxford University Press, American Branch, 1920.

PART V, Volume I, of this *Oxford Medicine* series may be said to deal almost entirely with methods of diagnosis and their application to clinical medicine. The first 66 pages are prepared by Dr. Barker, who has written a delightful essay on a subject which is of interest to every clinician. He describes for us the ideal methods of arriving at a diagnosis in the presence of some hypothetical condition. Dr. Baker is extremely thorough in his study of the patient, and shows us that to appreciate completely the normal and the abnormal of an individual is beyond the scope of any one man, and therefore it is necessary to depend upon others for the more special examinations. This brings up the question of the so-called group medicine, which Dr. Barker, needless to say, advocates most heartily. He particularly stresses that opportunity should be given the great middle class to benefit by such an organization of medical men. At the present time the cost of these examinations is prohibitive to people in the average walk of life, therefore combination should be formed which, by proper business methods, could carry on this work for nominal charges.

Dr. Henry A. Christian has written the succeeding ten pages; a general summary of the functional tests, which have proved of some value in medicine. This chapter is a short one, and as Dr. Christian says, it is chiefly to indicate the underlying principles and the scope of these tests.

Respiration in disease, the next chapter, is presented by Dr. Francis Peabody. This article will probably repay the reader by careful study, as it is upon a subject which we are not accustomed to consider carefully in disease, and yet withal it is a subject which is not only intensely interesting but also of great value in considering not only diseases of the lungs and disturbances of pulmonary function, but also in many other conditions.

The last chapter is by Dr. Du Bois. It is upon the subject of the study of diseases with calorimetric methods. As with the other authors in this present portion of Volume I, Dr. Du Bois

is a recognized authority in his subject. In fact, it is doubtful if there is anyone who could have prepared a more authoritative article than Dr. Du Bois, who has done a tremendous amount of research and investigative work in this interesting study of the heat production and loss by the body. The article describes the methods of calorimetry and their application to the study of disease in such a clear and lucid style that there can be no doubt but that all who read will understand this rather complex subject.

J. H. M., JR.

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A TEXT-BOOK OF DERMATOLOGY. By J. DARIER. Physician to the Hôpital Saint-Louis; Member of the Academy of Medicine, Paris, France; Honorary Member of the American Dermatological Association, etc. Translated from the second French edition. Edited with notes by S. Pollitzer. Pp. 769; 204 engravings and 4 colored plates. Philadelphia and New York: Lea & Febiger, 1920.

THE author has made the present volume as concise and practical as possible, while including the entire domain of cutaneous pathology. In order to make it short, he has sacrificed the entire bibliography, historical references, quotations, learned discussions, etc., limiting himself to the essential data from the standpoint of diagnosis and treatment.

The work is divided into two portions: Morphology of the Dermatoses and Nosology of the Dermatoses. The first twenty-two chapters are dedicated to the principal elementary dermatologic forms and to the syndromes derived from them. The author believes that the study of skin diseases should afford the first place to morphology—namely, to what can be seen. Eruptive dermatoses are first discussed from four angles: relating to efflorescence, to the eruption, to the disease and to the patient.

Under the name of elementary dermatologic forms, diseases of the skin of a variable morphology having various types of eruptive lesions on the one hand and of pathologic conditions of the skin on the other are discussed. Certain diseases having the same anatomic lesion, such as papules, vesicles, keratoses, etc., have been grouped together to show their resemblances and dissimilarities. Repetition would be a marked feature if the author had attempted to combine in contrast all the diseases of the skin having lesions of the same type as many conditions have a multiform eruption. In order to avoid this difficulty only the common and most characteristic syndromes are described in the first part of the volume, the others are mentioned briefly and their description follows in the second portion of the book.



Diseases such as eczema, lichen and psoriasis, the causes of which are multiple, complex or unknown, have been described in the first part of the work.

In the second part (Chapters XX to XXI) of the volume the pathologic entities, with a definite etiology, are classified according to the nature of their cause. The writer has placed the tumors of the skin under this heading, admitting that he conforms more to custom than following a personal conviction on the subject.

The arrangement of the volume, as is shown by the preceding description, is unique. The author states that, unfortunately, in the present stage of investigation the logical and scientific classification—namely based on etiology—cannot be followed.

The editor and translator, Dr. Pollitzer, of this work has added greatly to the elucidation by his expositions and additions.

Therapeutic notes are added as a separate chapter, giving the essential data required for dermatological treatment. A perusal of this section is interesting as showing the differences as to drugs and combinations as employed by the French and ourselves.

The text is good, the photographs excellent and the author is to be congratulated upon his work.

F. C. K.

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RAMBLING RECOLLECTIONS. By A. D. ROCKWELL, M.D. Pp. 332; 4 illustrations. New York: Paul B. Hoeber, 1920.

It is refreshing at times to browse in the fields of endeavor of a brother in the profession, especially one who is honest enough to tell of failures as well as of successes, of disappointments as well as of hopes fulfilled.

Dr. Rockwell's childhood and early youth are entertaining. One can then follow him through his student days. In the section of the book called "A Ride with Sheridan," is a rather vivid description of a young army surgeon in the Civil War. These chapters offer an opportunity for comparison and contrast with the experiences of those who served in the recent war. One chapter in the book deserves special mention, because it gives the history of electro-execution in which subject Dr. Rockwell was deeply interested and with which he had official connection, due to his reputation as a physician versed in the medical use of electricity. In the last section of the book one finds sketches about many well-known men with whom Dr. Rockwell came in contact.

A. G. M.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

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**Pathology and Treatment of Grip Empyemata.**—BEUST (*Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1920, xxxii, 94) says that grip empyema differs from the ordinary empyema in the greater virulence which is shown by the disease. This is seen in the rapid development of threatening symptoms and the high mortality. There is also a special inclination to fibrin formation, irregular temperature and recurrence of the primary lung affection. The abundance of fibrin formation hinders considerably the after-treatment of the empyema. The Bülow (suction) drainage is not sufficient alone to cause secure healing even if it is employed early, i. e., as soon as possible after the appearance of the suppurative pleurisy. However, the Bülow drainage is especially valuable in relieving patients who are in very bad condition because of the grip pneumonia and empyema. Cases in which there is an extensive discharge on account of the development of a pneumothorax may be prevented by a two-stage operation. After the employment of the Bülow drainage in the first stage the patients so far recover that after several days, usually four to eight days, they tolerate a thoracotomy with rib resection. Primary rib resection should be employed in all cases that are in a fit general condition. The pus contains much fibrinous masses and can be drained thoroughly only by such a thoracotomy with rib resection. The surgeon should be in charge of the case whether the Bülow or rib resection drainage is employed. In the most severe cases in which the grip empyema becomes suddenly threatening, the Bülow drainage may be employed by the medical man as an emergency measure to good advantage, provided the proper technic is employed.

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**Observations on Empyema.**—ASHMURST (*Annals of Surgery*, 1920, lxxii, 12) reports an excellent study of 43 cases of empyema and pays particular attention to the finding of concealed collections of pus and to dependent drainage. In his exploratory thoracotomy he places the patient in the fully prone position, under local anesthesia makes the

incision over the eighth or ninth rib and resects subperiosteally the desired length of the rib. As a rule 8 to 10 cm. is sufficient. The pleura is opened between forceps, like the peritoneum. The lung is usually adherent and does not collapse. Even if not adherent it seldom collapses to less than half its bulk, when the patient is lying prone, and there is comparatively little respiratory disturbance. Next inspect the structures closely. The lung may be so closely adherent to the diaphragm that it will be very difficult to recognize the line of junction. Wall off the rest of the pleural cavity with moist gauze. Then with fingers, dissecting forceps, or even knife and scissors (according to the density of the adhesions) the lung should be gently released. Usually it is well to clear the diaphragm first. If no pus is found here, the packs are rearranged so as to protect the lower part of the pleural cavity, and a search is begun in the fissures of the lung. The lung is absolutely insensitive to these manipulations. When pus is finally located and has been evacuated, a rubber tube (with a lumen of at least 1 cm.) surrounded with loose iodoform gauze is placed in the abscess cavity, the isolating packs are removed, and the wound is closed in layers, but not too tightly, around the drainage tract—the pleura and intercostal structures in one layer, and then the skin. He concludes that cases of pleural effusion suspected of being purulent should be punctured (with a hollow needle attached to a tight syringe) and if the effusion is massive most of it should be removed by aspiration one or two days before thoracotomy is undertaken. If the fluid found on puncture is serous or seropurulent, thoracotomy may usually be postponed, until frank pus has formed, as this delay will permit the formation of firmer adhesions and thus prevent complete collapse of the lung when the empyema is opened. Cures of such seropurulent effusions have so rarely occurred without final resort to thoracotomy that attempts to cure them by injection of antiseptic fluids into the unopened pleura are usually detrimental to the patient. If in a case of a suspected empyema the symptoms are urgent, but pus cannot be found by puncture, exploratory thoracotomy should be undertaken in an effort to locate and drain the pus. The operation of thoracotomy for empyema should provide free and dependent drainage, secured by the resection of a rib, usually the ninth, tenth or eleventh, in front of its angle. This operation may be done with perfect satisfaction to both patient and surgeon under local anesthesia, and in most cases this is preferable to a general anesthetic. Postoperative irrigations are unnecessary, unless after several months the lung shows no tendency to expand, when the use of Dakin's fluid may prove beneficial. In selected cases (those with small cavity) injections of bismuth paste may procure closure of the sinus. If the cavity cannot be made to heal by these means, the surgeon should do a major thoracotomy, combined with decortication of the lung and dissection of the pleura, and in some cases resection of a number of ribs to permit the chest wall to collapse in part and meet the expanding lung.

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**Some Principles Involved in the Treatment of Empyema.**—GRAHAM (*Surg., Gynec. and Obst.*, 1920, xxxi, 60) says that his appointment as a member of the Empyema Commission enabled him to observe an unusually large number of cases, and this opportunity was supplemented

by being placed in charge of 138 cases of chronic empyema at Fort Sheridan, Illinois, upon his return from France, in May, 1919. He has tested out by experiment the soundness of the principles advocated by this Commission and challenged by some as unsound. He summarizes his work as follows: The extensive recent literature on empyema reveals both a striking tendency toward more or less standardized treatment and a radical departure from methods in use prior to the war. He discusses the cardinal principles of (1) the avoidance of an open pneumothorax during the acute pneumonic stage of the disease; (2) early sterilization and obliteration of the cavity, and (3) the maintenance of the nutrition of the patient. In the normal thorax the mediastinal structures are so mobile that their resistance is negligible from the standpoint of pressure relationships so that the thorax can be considered as one cavity instead of two. Any change of pressure in one pleural cavity will manifest itself to practically the same degree in the other pleural cavity with the result that both lungs will be about equally compressed. The situation in this respect is the same in the dog as in the human, and, therefore, experimental results obtained on the dog can be directly applied to the human. The likelihood of a fatal asphyxia as a result of an open pneumothorax depends upon a number of factors, important ones of which are the size of the opening and the vital capacity of the individual. A mathematical expression has been devised by which it is possible in a given case to approximate the non-fatal opening in the chest wall if the vital capacity is known. One who has an average vital capacity (3700 cubic centimeters) and a normal thorax can withstand an opening in the chest wall of 51 square centimeters (8 square inches), but the individual of exceptional vital capacity (as, for example, 7100 cubic centimeters), can live with an opening of 101 square centimeters (15.6 square inches). A bilateral open pneumothorax is practically no more dangerous to life than a unilateral opening provided that in each case the areas of the openings are the same. These observations have a very important bearing on the question of open drainage of cases of empyema, particularly during the acute pneumonic stage when the vital capacity is low. After adhesions have formed and the mediastinum has become somewhat stabilized, both by adhesions and inflammatory induration, then the pressure relationships may be materially different on the two sides. Collapsing thoracoplastic operations have the disadvantage, even when successful, of apparently permanently reducing the vital capacity.

**Chronic Paroxysmal Trigeminal Neuralgia and Its Treatment.**—HARRIS (*British Med. Jour.*, May 22, 1920, 693) says that in the last twelve years he has had 312 cases. Only a comparatively small number get relief from drugs. Practically the only two methods of relief are gasserectomy and alcohol injections. The former operation should never be undertaken until alcohol injection has been thoroughly tried. During the last ten years Harris has injected the Gasserian ganglion 63 times. In 31 the anesthesia has remained total and no recurrence of pain has taken place. In many of the remainder partial ganglion anesthesia has persisted though pressure could be felt, yet the relief from pain appears to be equally good. In many cases, though total ganglion anesthesia is produced at the time of injection, yet the anes-

thesia of the first and second divisions wears off, perhaps completely, in from ten minutes to an hour, though the third division remains totally anesthetic. In such a case pain is liable to recur after two months or two years, as in a case of ordinary injection of a nerve. With total destruction of the ganglion there is the same liability to keratitis as with the operation of gasserectomy, but if the lids are kept carefully closed by strapping for the first week and the conjunctival sac washed out with boracic lotion twice a day, there will be little or no trouble. Hutchinson's partial gasserectomy avoids the danger of keratitis but is not a certain permanent cure, as Harris has seen three such cases relapse with neuralgia. In almost every case, as soon as anesthesia develops from the injection, the neuralgic pains cease, and they can no longer be started by any chewing movements or rubbing the face. The duration of the cure rarely lasts less than twelve months, if good anesthesia has been obtained, and in the majority the relief of pain lasts from two to three years. Very many of Harris' cases have been free for four or five years, one six and a half years, another seven years, another nine years after nerve injection only. No trophic effects on the skin are ever seen. Keratitis is a risk if the cornea is anesthetic after injection of the ganglion, but this may always be avoided by proper precautions.

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## THERAPEUTICS

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UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK,

AND

CHARLES C. LIEB, M.D.,

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**A Collective Investigation of 10,000 Recruits with Doubtful Heart Conditions.**—Report IV. Compiled by S. R. WELLS (*British Med. Jour.*, May 29, 1920, p. 730). The following is the author's summary: Taking aortic regurgitation and mitral stenosis as the two typical valvular lesions which can be diagnosed with comparative certainty during life, the results of the present statistical inquiry lead us to the following conclusions: (1) The most important etiological factor in the production of organic lesions of the heart valves in men between the ages of eighteen and forty-one is rheumatic fever. (2) Strain can independently produce aortic regurgitation. (3) While strain may be a cause of mitral stenosis, it is a much less important factor than in the production of aortic regurgitation. (4) There is a third agent giving rise to symptoms simulating influenza, which is an efficient cause of mitral stenosis, and can possibly affect the aortic valves as well, but is not nearly so likely to do so. We have been unable to find any statistical evidence that syphilis, scarlet fever, diphtheria, pneumonia, or gonorrhea, are causes of valvular lesions, nor can we find statistical evidence that a history of

growing pains points to affections productive of valvular lesions. The same may be said, with slight reservations, of a history of rheumatism where there is no clear account of pain, swelling of the joints, fever, or confinement to bed. The evidence in favor of chorea as an efficient cause of mitral stenosis is strong, and we have found some, though not very striking, evidence in confirmation of the view that chorea and rheumatic fever are both manifestations of the activity of a common cause.

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**Experiences with Luminal in Epilepsy.**—GRINKER (*Jour. Am. Med. Assn.*, 1920, lxxv, 588) found luminal in small doses (1.5 to 2 grains), once or twice daily, capable of arresting the convulsions of epilepsy. Larger doses are seldom required but may be given with safety. Large doses may be administered when beginning treatment, especially after sudden withdrawal of bromide treatment; even in such cases the dose may be gradually reduced to 1.5 to 2 grains. Luminal does not appear to be habit-forming and no harmful effects have been observed from its long-continued administration. Patients receiving average doses of luminal do not show the peculiar mental torpor of those taking bromides.

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**The Physiological Action of Fumes of Iodin.**—LUCKHARDT, KOCH, SCHROEDER and WEILAND (*Jour. Pharm. Exp. Therap.*, 1920, xv, 1). Iodin deposited on the skin in the form of fumes is absorbed and appears in the urine of both man and dogs. In dogs the iodine content of the thyroid was found to be greatly increased, the increase being accompanied by a corresponding change in the histological features of the gland. The same was true when the iodine was inhaled. The inhalation of iodine fumes causes respiratory disturbances consequent on the irritant action of the fumes; large amounts lead to the death of the animal within twenty-four hours from acute and rapidly developing pulmonary edema. The edema supervenes more rapidly in animals having respiratory disease than in normal dogs. The authors believe that the fumes of iodine should never be inhaled for therapeutic purposes and in persons with pulmonary disease such administration is absolutely contra-indicated.

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**The Stability of Digitalis-leaf Extracts. The Infusion (Second Paper).**—POMEROY and WEYL (*Am. Jour. Pharm.*, 1920, xcii, 394). A comparison of the relative activity of digitalis infusions and tinctures of equal concentration shows the infusion to be slightly less active. Placing a 20 per cent. limit on deterioration, the authors conclude that the infusions should be discarded in from three to five days' time; at lower temperatures the time limit may be extended to from six to seven days. In addition to the instability of the infusion itself, a wide variation in the strength of various samples of leaves was found. The addition of alcohol did not add to the stability of the infusion.

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**Botulism from Canned Ripe Olives.**—EMERSON and COLLINS (*Jour. Clin. and Lab. Med.*, 1920, v, 559). Within the last six months there have been at least five small outbreaks of botulism in this country, due to the eating of canned ripe olives. Four of the five outbreaks were due to *B. botulinus* of the Boise Type (Type A). While Dickson's

recent work has definitely demonstrated the protective value of antitoxin when administered soon after the toxin, it must be remembered that antitoxin for one type is specific for that type alone. The authors recommend adequate government supervision of the plants (including fish packing and canning plants) for protection against *B. botulinus* contamination.

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**Gastric Response to Foods. X. The Psychic Secretion of Gastric Juice in Normal Men.**—MILLER, BERGEIM, REHFUSS and HAWK (*Am. Jour. Physiol.*, May, 1920). The sight, taste and smell of appetizing food was found to give rise to a distinct secretion of gastric juice in normal men. Evil odors depressed secretion. Nourishing foods unpleasantly prepared and served sometimes caused a slight delay in evacuation time but none in acid response. The ultimate utilization of the protein of a diet prepared in a most unpalatable manner was not found to be appreciably less than that of the same diet served under the best conditions. Anxiety and mental strain markedly delayed gastric digestion.

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**Gastric Response to Foods. XI. The Influence of Tea, Coffee and Cocoa upon Digestion.**—Water, tea and coffee, in 1 liter amounts, were practically without effect on the evacuation time of a uniform mixed meal; the rise of the level of intragastric acidity was somewhat delayed, as compared with the basal meal alone. Cocoa, in 1 liter amounts, distinctly delayed the evacuation time and the development of intragastric acidity. Tea and coffee in these amounts caused acceleration of the heart-rate, vasomotor relaxation, tremors, etc. Urine secretion after tea or coffee ingestion varied from 550 to 860 c.c.; after cocoa, from 125 to 370 c.c.

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**Vitamine Studies. V. The Antiscorbutic Properties of Raw Beef.**—DUTCHER, PEARSON and BIEST (*Jour. Biol. Chem.*, 1920, xlii, 301). Water extracts of raw, lean beef did not delay the onset of scurvy or increase the length of life of guinea-pigs fed on a "scorbutic" diet. Orange juice prevented scurvy, whether meat extract was fed or not. From the excellent condition of the animals on the orange-juice beef extract diet, the authors conclude that the scurvy was due rather to the absence of the antiscorbutic vitamine than to any deleterious property of the beef extract.

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## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

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**Sino-Atrial Heart Block in a Child.**—BROWN (*Arch. Int. Med.*, September, 1919) discusses the case of a boy aged eleven years, in whom there was found the arrhythmia, which is usually called sino-auricular

block. There was a complete standstill of the entire heart for one or more beats, the intermissions being separated by from one to six normal cardiac cycles. The blocks which characterize the records from this patient may have hypothetically resulted from a failure of the sino-atrial node to generate an excitation wave, from a failure of the atrial musculature to respond to the excitation, or from interference with the impulse in its passage to the atrium. The persistence of a fundamental rhythm underlying this arrhythmia was the evidence of the maintenance of rhythmic impulse production. There was no evidence of diminished atrial excitability, and the atrium responded to every excitation wave when the rate was much augmented. The arrhythmia was best explained by the existence of some factor which interfered with the transmission of correctly timed excitation waves. Such a functional defect may be dependent either on structural changes or the influence of the depressor nerve. The records from this case presented some of the characteristics of functional block due to structural changes. After several contractions an impulse failed to pass. In the series of normal beats the atrial cycles preceding an intermission were slightly longer than those which followed it. This suggested an increasing delay in impulse transmission prior to the appearance of the block. Sinus arrhythmia associated with sino-atrial block is due to a progressive delay in impulse transmission according to Levine. Were this hypothesis applicable in this case a retardation in the rate of impulse production would eliminate and an acceleration would increase, the block. The rate was reduced and the block was eliminated by holding the breath after deep inspiration, but when stronger vagus stimulation was employed directly by pressure on the right vagus, or indirectly by ocular pressure, the intermissions increased in frequency. The administration of  $\frac{7}{5}$  grain of atropin increased the rate to 120 per minute, but with acceleration the blocks disappeared. It was evident that if there was any structural defect in this case, it was a minor factor, and that the abnormal rhythm was due chiefly to vagus influence. The action of small doses of atropin in eliminating the arrhythmia without producing sufficient vagal inhibition to permit the acceleration of the impulse production, and the persistence of this slow, regular rhythm were of clinical interest. They indicate a prolonged primary atropin effect, which moderately stimulates the vagus center and retards impulse production, while coincident with this is a selective peripheral action of atropin on the vagus endings, which control impulse transmission, thus facilitating the passage of excitation waves to the atrium.

**Mental Changes in Children of Germany.**—BLANTON (*Mental Hygiene*, July, 1919) reports that at least 40 per cent. of the children in the Volksschulen of Trier, Germany, are suffering from malnutrition of such a degree as to cause a loss of nervous energy. There was no increase in the percentage of cases normally found of neuroses, psychoses, abnormal nervousness, organic nervous disease, ties, or conduct disorders. There was an increase of the number of borderline defectives totaling not more than 1 per cent. of the total school population. There was no increase in the percentage of the speech defects, especially stuttering, normally found, but there was a marked increase in poor lisping slurring speech due to the retardation or interference with the



fine coordination necessary for good speech, caused chiefly by malnutrition. The percentage of children failing to pass their grades was increased from an average of 8 per cent. in pre-war times to 15 per cent. in 1917 and 1918. About half of this 1 per cent. increase in retardation was due to malnutrition and the other half was due to war conditions. There was a lowering of the whole standard of school work caused chiefly by malnutrition, but partly by war conditions in general. Half of the children who in pre-war years did superior work, now do average work and the percentage of children who do inferior work was increased from 20 per cent. to more than 30 per cent. The specific changes noted in the children caused by malnutrition were: inattention during school hours; a lack of nervous and physical energy; poor and slow comprehension for school tasks; poor memory for school work; general nervous restlessness while in school. Children of good nervous stock and of superior or good average intelligence can withstand malnutrition of even a serious degree extending over more than two years without any impairment of the intelligence or any definite emotional change; a lack of nervous energy was about all the change that occurred. Those of poor nervous stock with poor or inferior intelligence suffer a general and sometimes a permanent lowering of the whole intelligence from even a moderate degree of malnutrition. Not more than 5 per cent. of the total school population suffered injury to the nervous system such as to affect the intelligence permanently. Conditions in Trier were not typical, having been worse than those in general throughout the Rhenish province as judged from the condition found in the cities of Cologne, Coblenz and Bonn.

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**Calcium Metabolism of Infants and Young Children and the Relation of Calcium to Fat Excretion in the Stools.**—HOLT, COURTNEY AND FALES (*Am. Jour. Dis. Children*, February, 1920) estimate that the average of calcium oxid by healthy infants taking modifications of cow's milk is 0.09 gm. per kilogram of body weight. Since the average absorption of calcium oxid by breast-fed infants is about 0.6 gm. per kilogram of body weight, it may be assumed that 0.06 gm. per kilogram of body weight is the minimum normal absorption by infants taking modifications of cow's milk. The daily average total excretion of calcium oxid in the stools range from 0.34 to 1.06 gm., with a mean of 0.70 gm. The excretion and the absorption of calcium were in general dependent on the amount of calcium intake, from 35 to 55 per cent. of the intake being absorbed. To insure the average absorption of 0.09 gm. of calcium oxid per kilogram, the intake of calcium oxid should be at least 0.19 gm. per kilogram and to insure absorption equal to the average found for breast-fed infants the intake should be at least 0.13 gm. per kilogram. The best absorption of calcium was obtained when the calcium intake bore a definite relation to the fat intake, or when the food contained from 0.045 to 0.060 gm. of calcium oxid for every gram of fat, and when at the same time the fat intake was ample, not less than 4.0 gm. per kilogram. An excessive calcium intake apparently did not increase the calcium absorption, the excess being excreted. When the intake of calcium oxid was very low, less than 0.10 gm. per kilogram the absorption of calcium oxid was less than the normal calcium requirement of the body. The total absorption of calcium oxid

varied in general with the weight of the child; the per kilogram absorption did not vary regularly with either the age or the weight. The relation of calcium excretion to soap excretion was not constant. The excretion of soap was directly related to the type stool, that is, to the water content and to the reaction of the stool. The excretion of calcium was closely related to the calcium intake. On the average, the normal and the constipated stools, with high soap content, were found when the intake of calcium was high; and they showed the higher excretion of calcium. Constipated stools, which contained more soap than normal stools, had lower calcium content. Non-homogeneous stools, with the lowest average soap content, showed the same amount of calcium not held as soap as did the constipated stools, with the highest soap content. The calcium that could be lost as soap was never a large proportion of the calcium intake. Even in the stool containing the most soap it was found to be less than three-tenths the calcium intake. The calcium lost as phosphate was shown not to be increased in soapy stools. The calcium percentage of the total solids varied with the water content of the stools, diminishing as the water increased. The calcium absorption was much lower when diarrhea was present. With an increased excretion of calcium in diarrheal stools, there was a marked decrease of soap excretion. The calcium of absorption by rachitic infants was much lower than in healthy infants. In the few cases in which the authors made observation on infants recovering from rickets, the calcium absorption was higher than the average. The infants had received cod-liver oil for a considerable time. The administration of cod-liver oil regularly increased the absorption of calcium, unless diarrhea was present.

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**Atropin Treatment of Pylorospasm and Pyloric Stenosis.**—HAAS (*Arch. Ped.*, October, 1919) says that hypertrophic pyloric stenosis is probably only an advanced degree of pylorospasm. Both of these conditions are seen in the syndrome of hypertonia or in the hypertonic infant. The cause is probably in a disturbance of the physiologic action of the vegetative nervous system. This is made up of two parts, the autonomic and the sympathetic. These are normally in balance, but in this condition there is an overaction of the autonomic and there arises a condition of vagotonia. Although this is usually the case, there also occasionally exists a true organic stenosis of the pylorus. Many brilliant results have been obtained by the Rammstedt operation, but in this condition an operation should be rarely required and should only be done after atropin has been given a trial. When properly used this has been regularly effective in producing a cure. At present most authorities agree that hypertrophic pyloric stenosis and pylorospasm are two different clinical entities. In favor of this view is the existence of a cartilaginous hard mass of the pylorus in cases of stenosis, and the persistence of this mass long after a cure has been obtained by operation or otherwise. Among the arguments for non-medical treatment is the sudden death which not infrequently occurs. These are usually thymus deaths, and occur in cases operated as well as in those treated medically. Atropin is the logical treatment in these cases owing to its paralyzing effects upon the vagus nerve endings. There must be borne in mind that atropin is inconstant in value, resembling digitalis

in this respect. It deteriorates rapidly, and it must be used in doses sufficiently large to be effective. A common dose for an infant of this type from a few weeks to a few months of age is  $\frac{1}{30}$  to  $\frac{1}{25}$  grain in twenty-four hours, with an extreme of  $\frac{1}{10}$  grain divided among the days' feeding. A solution  $\frac{1}{1000}$  is used beginning with one drop and increasing rapidly until effective. The most frequent toxic symptoms are flushing, midriasis, dryness, which disappears promptly when the drug is withdrawn. No danger exists even when these symptoms are present.

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## OBSTETRICS

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### Pregnancy and Labor following Amputation of the Cervix Uteri.—

AVLIK (*Surg., Gynec. and Obst.*, August, 1919) writes a paper upon this subject in which he quotes the experience and opinions of various obstetricians, all tending to show that amputation of the cervix is followed during pregnancy and labor by complications of varying severity, which may even require the performance of Cesarean section and labor for the safe delivery of the patient. He describes the case of a woman, who had a very difficult confinement, in which pubiotomy was done and a twelve-pound child extracted that lived twenty-four hours. The patient was badly torn and six months later the cervix was amputated. This patient came under observation in the fourth month of her third pregnancy. The cervical scar was a hard, inelastic ring which did not soften. Fearing that the patient would go into labor with a disastrous result, Cesarean section was performed about two weeks before full term. The patient was sterilized by resection of the Fallopian tube before the abdomen was closed. Mother and child made a good recovery. He also describes the case of a woman who had a very difficult forceps delivery, followed by abortion and afterward by the amputation of a badly lacerated cervix. Since this operation she had three abortions at six and a half, four and three months. When seen she was in the third month of her sixth pregnancy and shortly afterward aborted. At the time of writing the patient was again about two months pregnant and refused operation and sterilization. The study of statistics shows that sterility is not uncommon after amputation of the cervix; further, less than 20 per cent. of these patients conceived after the operation. These results are cicatricial contraction, stenosis at the internal os and perhaps other changes. It is estimated that 5 per cent. of these patients abort when pregnancy follows the operation. Sixty-four per cent. had serious dystocia while in 128 cases but four had easy labors after the operation. Unquestionably the cervix has a function in closing the uterus at its lower extremity and thus preventing premature evacuation. The absence of this safeguard may

well explain the frequency of abortion after the cervix has been removed. Studiford recommends that if amputation be done during the child-bearing period the operation should not extend higher than half an inch below the internal os. This would exclude the original technic of Schroeder. In discussion, Paddock stated that in his experience abortion had occurred most frequently from the diseased condition of the endometrium rather than the anatomical change produced by the operation. He could not believe that abortions which occurred early are due to amputation of the cervix. He could well see how amputation could produce premature labor. In his experience labor at term without serious complications have followed the operation. Heany called attention to Martin's operation, which is a low amputation, with just a portion of the cervix removed. He has seen successful labor follow this operation twice in the same patient. In the experience of the reviewer premature labor developed in a case in which amputation of the cervix had been done. Spontaneous dilatation failed and it was necessary to complete dilatation by artificial methods. In the second case there was long delay in the first stage; labor was finally terminated by manual dilatation and extraction by forceps. In two other cases Cesarean section was the only means of successful delivery, because the mass of cicatricial tissue of the cervix made delivery through the cervix impossible.

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**Influenza Complicating Pregnancy.**—HARRIS (*Jour. Am. Med. Assn.*, 1919, No. 72, p. 978) has studied 1350 cases. This number did not include the very mild cases or many which occurred during the first months of pregnancy when the pregnant condition might readily escape detection. It was found that pneumonia complicated the influenza in about half of the pregnant patients. In these cases complicated by pneumonia the mortality was about 50 per cent. and this was seen especially during the last three months of pregnancy. The average mortality of all cases was 27 per cent. Pregnancy was interrupted in 26 per cent., and of these 52 per cent. developed pneumonia, abortion or premature labor. Thus in 38 per cent. of the fatal cases the patient died without the interruption of pregnancy, while in 62 per cent. of the pregnant cases pregnancy was interrupted. When pregnancy was not interrupted the mortality-rate was 16 per cent. When interruption occurred it rose to 41 per cent.

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**The Development of the Mammary Glands.**—MEYERS (*Am. Jour. Dis. of Children*, 1919, No. 18, p. 4) calls attention to the development of the mammary gland in the embryo. It is first represented by a single layer of elongated epithelial cells extending on each side from the anterior to the posterior limb bud. By the proliferation of these cells resulting in the formation of several layers the mammary line is formed, slightly elevated above the epidermis. The growth of the cells continues only at intervals along the line. The intervening portions of the line gradually disappearing, and as the hillocks grow they sink into the subjacent tissue and begin to bud from their deeper surfaces. The buds which develop progressively and sink into the mesenchyma represent the future milk ducts. In men there are 15 to 20 primary buds in

each hillock. The lumen of the milk duct in man develops about the sixth or seventh month, caused by a rearrangement of cells. The lumen of the milk duct in man begins to develop about the sixth or seventh month, and is formed there by a rearrangement or by degeneration of cells. At birth the ducts show congenital branching and soon after birth secretion of milk appears in the milk ducts of human infants. This secretion, which may cause marked engorgement, is usually carried away by leukocytes or direct absorption within the next twenty days. In children prematurely born fluid may be present at birth and may not appear for many days or not at all. This contains all the constituents of true milk, but it has not been determined whether the stimulus which induces activity in the mammary glands of the mother is the same as that which excites the glands of the newborn to secrete what is called "witches' milk." The stroma of the mammary gland develops from remnants of the mesenchyma about the mammary hillocks. As these sink into the surrounding tissue their superficial surface becomes depressed below the level of the surrounding epidermis by a process of degeneration and a desquamation by which is formed the mammary pit. Very soon a small papule forms at the base of the pit, which is the beginning of the nipple, and this grows until it fills the pit. In many cases the nipples of newborn infants have not reached the surface of the surrounding epidermis. In others they fill the pit completely while in the remainder they are slightly elevated. Usually the nipples become elevated shortly after birth and are of adult form and size at puberty. In man each of the fifteen to twenty milk ducts has a separate milk core in the surface of the nipple. In 7 per cent. of human embryos supernumerary mammary glands develop along the course of the original mammary stream. In the lower animals the period of anemia and depression at an early age stops for a time the development of the mammary glands. When the animal is fed well the glands respond slowly. If the sexes be compared it is shown that "witches' milk" is secreted by both; up to puberty the milk ducts branch somewhat more in the female than in the male, and that in the male the mammary gland may show some growth after puberty while retrogressive changes are more apparent in the male gland after the thirtieth year.

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**Fats, Cholesterol and Sugar in the Blood During Pregnancy.**—SCHILLER (*Surg., Gynec. and Obst.*, November, 1919) has studied thirty pregnant patients, examining their blood to determine the presence of fat, cholesterol and sugar. He finds that in the later months of pregnancy, or in the first two weeks of the puerperal period, there is no hyperglycemia. The glands of internal secretion and the kidneys offer an explanation for glycosuria and alimentary glycosuria. Where in pregnancy a patient grows excessively fat this is for the most part a condition of hyperlipoidemia. There is no direct parallelism between cholesteremia or the hyperglycemia of pregnancy. It is probable that the endocrine glands are to be considered an important factor in developing the action of the mammary glands. On one occasion, in the case of a patient nursing her infant, the breasts became unusually swollen and the mother succeeded in nursing her child. It was observed that nursing caused great irritation, and that gradually the mother was

becoming much excited and complaining constantly of the breasts. The secretion of milk was not very abundant. Finally fever developed, although the infant remained remarkably undisturbed. Thyroid extract was given the mother in full doses when her symptoms disappeared and mother and child did well. This is in keeping with the remark of the writer that the endocrine glands are responsible for many conditions pertaining to lactation.

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## GYNECOLOGY

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**Disagreeable Sequelæ from Radium Treatment.**—GRAVES (*New York Med. Jour.*, 1920, cxi, 969) recounts certain disagreeable sequelæ from intra-uterine radiation which, though mentioned by several writers, received minor attention or have been lost sight of in the reports of brilliant end-results. Some of these symptoms are significant chiefly from the psychological influence which they may exert on the patient, but even these may be of considerable import to the patient's general welfare. First among the specific symptoms from an intra-uterine application of radium must be mentioned nausea and Graves calls attention to our statement that "nausea and vomiting are the exception rather than the rule after radiation." His own experience has been rather the reverse for he finds that the majority of patients suffer more nausea than would be expected after a simple ether examination and curettage, in which the length of anesthesia would be approximately the same. That the nausea is due to something more than the simple effect of the anesthetic is often strikingly evident by the almost immediate relief that follows the removal of the radium in certain cases. In other cases the nausea has been persistent, with greater or less intensity, for a period much longer than is seen in even unfavorable cases after a short anesthesia, where radium has not been used. In some cases there is little or no nausea after radiation, but in his experience these cases are the exception, whereas after a simple curetting they are the rule. In one of his patients violent nausea and vomiting persisted for seven days after a mild dose. The patient, a strong young woman of twenty-seven, was neurotic and apprehensive, but the severity of the symptoms could not be explained wholly by her mental attitude, nor by the small amount of ether administered at the operation. A second important after-result of the radium treatment is a possible continuation or reappearance of the bleeding, for the cure of which the operation was

undertaken. Such bleeding may appear within a few hours after the removal of the radium, and may persist for days or sometimes weeks, with varying degrees of intensity and constancy, before permanent cessation takes place. The amount of blood lost varies from a steady profuse flow to an occasional scanty showing, and the time of its appearance may extend from two or three days to five or six weeks. To a nervous, apprehensive woman, not premonished of this possible event, and confidently expectant of an instantaneous cure, the continuation of symptoms comes as an alarming shock, and the attendant who has neglected to forewarn his patient finds it extremely difficult to explain conditions. In some cases, in patients treated for menorrhagia, the next one or two periods may show no diminution, and sometimes even an increase of the catamenial flow. Here again the attendant who has not cautioned his patient finds himself in an embarrassing predicament in his perfectly truthful assurance that the ultimate result will probably be entirely satisfactory. A third specific after-effect of intra-uterine radiation is leucorrhea. In cases of recurrent bleeding it seems to appear as the end-result of the flow in the form of a thin watery discharge of a pinkish hue which gradually fades to a pale brown or colorless character. In cases where the radium application has caused a complete cessation of bleeding the same watery discharge usually ensues for a varying length of time, lasting from a few days to several weeks or months. Some patients do not notice it at all but they are in the minority. It has been a matter of rather frequent personal observation that this characteristic radium leucorrhea appears periodically for several months at the usual menstrual time and seems to indicate an effort on the part of Nature to reestablish the menstrual rhythm. The discharge is chemically irritating and if not properly treated by cleansing douches becomes foul and may set up an annoying vaginitis, as has occurred in more than one of his cases. Pelvic pain has been described by some as one of the typical symptoms following the radium treatment. There are occasional complaints on the part of patients of a slight nagging pain in the side, usually on the left, which has subsided in a few days and gives no further trouble. In a small number of cases patients suffer pain of a nature of a uterine colic during the time of the radium application, the result apparently of a reaction on the part of the uterus to a foreign body within its cavity. In a few other cases, however, the pain experienced during the immediate convalescence proved to be the forerunner of later very serious inflammatory consequences. In the light therefore of present experience, Graves is convinced that in the properly selected cases there should be no adnexal pain and that if it does occur, it must be regarded as a danger signal of grave import. Too great emphasis cannot be laid on the danger of making intra-uterine radium applications in the presence of pelvic inflammation. Even though the active inflammatory process existed years before and there remain only a few peritoneal adhesions radiation is attended with risk. Inasmuch as an old inflammatory process is sometimes missed both in the history and the most expert preliminary examination, it stands to reason that even with great care occasional results are sure to be encountered and anyone who says that the intra-uterine application of radium for bleeding is attended with no danger knows little whereof he speaks. The injurious influence of radium on chronic inflammatory

pelvic conditions, is perhaps the most important reason why in the extensive clinical use to which radium is destined very soon to be put, its employment, in gynecological practise at least should be limited to responsible and well trained operators. Some mention has been made in the literature of a reaction on the part of the kidneys to radiation. Graves has had an opportunity of observing in another clinic, the onset of an acute nephritis following an intrauterine treatment, in the case of an elderly woman who had a cardiorenal history. He has collected no specific data on this point in his series of cases, nor has he seen any systematic report throwing light on this subject. Nevertheless, there is sporadic evidence that caution should be exercised in treating cases with renal disease. Nervous symptoms following radiation are of peculiar interest. If the menses are inhibited, hot flushes are common but not constant. They occur in about the same proportion as after hysterectomy with or without the ablation of the ovaries. Some think they are less intense and annoying, others think they are more so. In his experience he cannot see that there is any marked difference one way or the other. They seem to follow the same law as after radical operations in that they are intensified by complicating discomforts and temporary disappointment over the result of the treatment. The influence of the ovarian secretion is strikingly illustrated in cases where, after a period of amenorrhea, the menses are reëstablished with a complete synchronous disappearance of hot flushes. As after hysterectomy, the hot flushes when present are usually amenable to ovarian therapy, preferably in the form of the residue or the whole extract. The various points brought out in this article are presented not for the purpose of depreciating the great value of radium in the treatment of non-malignant uterine hemorrhage, but rather to warn those who have not yet used it for this purpose that the immediate convalescence from a given treatment is by no means always a bed of roses.

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## OPHTHALMOLOGY

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Action of Hypophysin (Pituitrin) Upon the Pupil of the Rabbit.—POLLECK (*British Jour. Ophthal.*, March, 1920, p. 106) finds that hypophysin (pituitrin), when instilled into the eye of the rabbit, produces a mydriasis in about 94 per cent. of the experiments, although it is necessary in some cases to repeat the instillations several times. The effect is increased by decentralization (*i. e.*, cutting the sympathetic in the neck below the superior cervical ganglion) and still more by



deganglionation (excision of the ciliary ganglion and accessory ganglia and the superior cervical sympathetic ganglion of the dilator pupillæ or of the sphincter pupillæ) and most markedly by deganglionation of both dilator and sphincter pupillæ. When hypophysin is administered by intravenous injection, the local mydriatic effect is lost if the blood-pressure is raised, when a miosis occurs, due to central stimulation of the third cranial nerve which relaxes with the return of the blood-pressure to normal, and is followed generally by slight dilatation. The constriction of the pupil may be preceded by a brief dilatation due to excitement at the moment of injection. When the third cranial nerve is interrupted by section above the ciliary ganglion and accessory ganglia, the pupil dilates within a few minutes of the injection and generally returns to its normal size within an hour. Hypophysin acts on the same structure as adrenalin, and since adrenalin acts on the neuromyal junctions, hypophysin must also act there. Since deganglionation does not cause degeneration of the terminal plexus, the presumption is that both drugs act upon this.

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**Experimental Study of Antigonococcic Serotherapy.**—TERRIEN, DEBRE and PARAF (*Arch. d'Ophthalmol.*, June, 1920, p. 326) finds that injection into the anterior chamber of rabbits of an emulsion of gonococci causes an inflammation characterized by an iridocyclitis, torpid in evolution, with moderate pericorneal injection, but with great tendency to exudation, synechia and large hypopyon. The process continues from ten to fifteen days, terminates in total occlusion of the pupil with exudation into the pupillary field and partial cloudiness of the cornea. In a very small number of instances, the affection is milder as shown simply by a few synechia of the pupillary margin and slight discoloration of the iris with slight pericorneal reaction and little or no hypopyon. In rarer instances still, the disease is much more severe, manifesting itself by extreme reaction with considerable hypopyon, sometimes even perforation of the cornea and phthisis bulbi. The gonococci do not proliferate in the lesions noted, as, in fact, has also been remarked by various authors. Injection of 0.3 c.c. specific serum into the anterior chamber, twenty-four hours after preliminary inoculation, entirely modifies the evolution of the malady; the gravity of the lesions is much diminished, cure much more rapid (four to six days) and complete. Intramuscular, intravenous and subconjunctival injection of the serum is without influence upon the evolution of gonococcic ophthalmia; intra-ocular injection of antimeningococcic or antidiphtheritic serum is likewise inefficacious. The preventive power of the serum is doubtful; effects of intra-ocular injection twenty-four hours preceding injection of the microbes is uncertain. The favorable results of antigonococcic therapy confirm the observation previously made by these observers with the serum of immunized rabbits; but they do not justify any opinion upon the effects of serotherapy in man; in the case of the rabbit, the gonococci did not proliferate and the effect of the serum is reduced to an anti-endotoxic action.

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**Irregularity of the Pupil in Syphilis.**—RASQUIN (*La Clin. Ophthalmol.*, June, 1920, p. 292) has studied the occurrence of irregularities of the pupil in syphilis. He attributes the greatest importance to the form

which the irregularities take—the form of widely extended angles, for the following reasons: this form represents a morbid entity which may be present in all stages of the disease. It is also the most frequent, constituting 79 per cent. of all syphilitic irregularities of the pupil. It also gives the minimum percentage of failures in determining the syphilitic origin of pupillary irregularities; of 100 patients affected with this form of irregularity, syphilis was certainly present in 74 and possibly in 89. He is of the opinion that this form of irregularity, particularly when bilateral, as an almost certain symptom of syphilis so that when present the serological reaction should always be sought.

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**Raising Ocular Tension.**—LAGRANGE (*Annal. d'Oculist.*, July, 1920, p. 447) has attempted to raise the tension in eyes affected with high myopia and detachment of the retina. He has found in 17 of 52 myopes hypotension reaching 5 mm. Hg. After treatment normal tension supervened lasting several years in two-thirds of those operated upon. His procedure seeks to abolish the conjunctival meshes opposite the angle of filtration. This can be accomplished by repeated injection of cyanide or by a technic which he advocates and which consists in the destruction of the zone of conjunctiva surrounding the cornea adjacent to the anterior chamber, by cauterizing the tissues with the galvanocautery to bring about reaction and the production of a fibrous tissue. Hypertension usually supervenes the following day and lasts three or four days to give place to a renewed diminished tension, lasting a month, to be followed at the end of three or four months by increased pressure which finally becomes about normal. Fifteen cases of retinal detachments thus treated were cured.

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**Relation of Diseases of the Eye to Those of the Nose and Sinuses.**—STEIGER (*Med. Klin.*, 1920, No. 9, p. 221) calls attention to the multi-form and frequently intimate relations between diseases of the eye and those of the nose and accessory sinuses. Acute and chronic catarrhs of the conjunctiva often point to changes within the nose, which latter depend upon mechanical interference with normal nasal respiration, especially hypertrophy of the inferior turbinate. Scrofulous affections of the cornea and conjunctiva almost invariably indicate concomitant adenoid disease. The author believes that in such cases the symptoms are not simply concomitant, but that the nasal affection is to be regarded as the primary cause and as aggravating the ocular conditions; when the local symptoms of the nasal process are relieved, the ocular affection pursues a more favorable course. Acute inflammatory diseases of the orbit are due, in the majority of cases, to direct contact or conduction from an acute inflammatory process in the nasal fossæ. Frontal sinus, antrum, anterior and posterior ethmoidal cells and the mastoid may become involved whenever the narrow outlets of the nasal fossæ have been closed by disease, particularly acute swelling. Treatment consists accordingly in endo measures looking to prompt drainage of the diseased nasal fossæ. In chronic conditions, on the other hand, an independent focus of disease is frequently present in the sinuses, which is capable of further extension through erosion of the bones. Rational therapy demands removal of the primary focus of the affected sinus. Diseases of the lacrimal canal and sac may be excited by

swelling in the region of the inferior turbinate, whenever such swellings extend to and close the nasolacrimal outlet; dilatation of the latter also, as in ozena, may likewise cause disease of the lacrimal drainage apparatus through entrance of diseased products from the nose mechanically or by extension through continuity. The treatment in these cases is cure of the nasal affection. Dislocation of the globe by mucocoeles and tumors are too well known to require special mention; the same is true of affections of the optic nerve. The possibility of reflex neuroses of the eye of nasal origin should also be borne in mind; proof of the rhinologic origin of cataract, glaucoma, etc., has not yet been furnished.

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## PATHOLOGY AND BACTERIOLOGY

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**Streptolysin.**—Although the use of the blood-agar plate for the differentiation of alpha and beta hemolytic streptococci has become quite general, there has been a lack of uniformity of method and but little attempt at standardization. Impressed by the fact that the hemolytic zones surrounding colonies of the beta hemolytic streptococcus were wider and clearer on 10 per cent. sheep's blood-agar plates than on those prepared from similar concentrations of rabbit and human blood, DE KRUIF and IRELAND (*Jour. Infect. Dis.*, 1920, xxvi, 285) have studied hemolysin production by these organisms on blood accessible to general use, in order to ascertain whether variations in suitability exist among these bloods and to determine their optimum concentration for maximum production. Beef-infusion broth was employed in all cases, being adjusted to a hydrogen-ion concentration of pH 7.8. The investigations included studies on human, rabbit, sheep and horse blood. Instead of following the previously described methods of titration of filtrates or whole cultures the authors titrated the supernatants of early broth cultures seeded with from eight to twenty-four-hour cultures of hemolytic streptococci against constant quantities of the washed erythrocytes. Extensive experimentation was carried out, the results being recorded by tables and graphs. It was found that lysin production reached its maximum for the strains studied at a very early period in the life of the serum broth culture. When the serum broth was inoculated with young (eight to twelve hours) cultures this peak was reached in from seven to eight hours. In older cultures the crest may be deferred to twelve hours. Heated serums were usually superior to unheated ones. Sheep and horse serum were superior in all concentrations to human and far superior to rabbit serum broth. From the results of their experiments the authors devised a new blood-agar plate with the idea of using the optimum serum concentration for maximal lysin production of a blood both efficient and available. Sheeps' blood

was recommended, the serum-cell mixture being made by adding 1 part of cells to 4 parts of heated serum. This mixture was then combined with liquid agar in the proportion of 1 to 3, so that the final concentration was serum, 20 per cent.; cells, 5 per cent.; and agar, 75 per cent. This medium was found to be not only suitable for demonstrating the hemolytic zones of beta streptococcus but efficient in exhibiting the multiple concentric zones of green production and hemolysis for alpha streptococcus and pneumococcus.

**Experimental Streptococcus Empyema; Attempts at Prevention and Therapy by Means of Vaccine and Serum.**—The importance of streptococcus empyema has not only not decreased but has become intensified during the last year or so by its occurrence as a fatal sequel to influenza as well as in its previous relation to spontaneous bronchopneumonia and bronchopneumonia after measles. GAY and STONE (*Jour. Infect. Dis.*, 1920, xxvi, 265) undertook the present study not simply in an effort to proceed toward a possible practical method of treating streptococcic empyema, but in a desire to contribute some information to the larger question of streptococcic immunity as a whole. The experiments were conducted on rabbits by means of a single pure strain isolated from the lung of a fatal case of bronchopneumonia complicated by empyema and pericarditis, and though culturally of the *S. pyogenes* group, was immunologically unclassified. Beef infusion broth, pH 7.2 to 7.4, and containing either 1 per cent. glucose or 5 per cent. sterile fresh rabbit serum, was the medium employed. In counting the bacteria it was found that the Wright method, when checked by the gravimetric tests, gave accurate and consistent results. The particular strain was not markedly pathogenic for rabbits by intravenous inoculation. Attempts to increase the general invasive properties of the cultures for rabbits were unsuccessful, as were all attempts to produce bronchopneumonia by bronchial insufflation. Empyema could be procured, however, by injecting small quantities of broth cultures into the pleural cavity, particularly when subcultures from the pleural fluid of an animal with fatal empyema which had been passed through the pleura of several animals was employed. Death occurred in from one to seventeen days, the average being five days. Of 103 rabbits injected by a constant dose of a uniform passage culture, 102 showed involvement of one or both chests, with or without pericarditis. There was no evidence of an elective localizing affinity with the strain used. If sufficient amounts of killed and subsequently living cultures of streptococci were given over a considerable period of time, protection against empyema occurred. The total number of bacteria injected, rather than the number of injections, seemed to be the decisive factor. The immune serums produced gave positive agglutination reactions at 55° C. in dilutions of from 1 to 400 to 1 to 12,800. The technical difficulties were surmounted by using a constant homogeneous suspension, made by the addition of phenol in a final concentration of 0.2 to 0.5 per cent. to a twenty-four-hour serum broth culture. The serum of the animals in which active immunity had been proved by intrapleural inoculation was found to vary in tropin content from five to eighty times that of normal rabbit serum. Satisfactory precipitin reactions were obtained

by the immune serums used for therapeutic purposes, the antigens consisting of extracts of ground and dried streptococci. It was shown that the immune sera which contained strong antibodies may have a preventive and curative action when given before, with and after the infecting intrapleural dose of bacteria. Attempted vaccine therapy of the localized empyema gave consistently negative results. The authors conclude that although distinct results in the prevention of experimental empyema and, in rare instances, the cure of empyema may be produced by the use of immune serum from rabbits, they have as yet no evidence of an encouraging serum therapy to offer and that no optimistic conclusions can be drawn from their results as to the possibility of protecting human beings against localized streptococcus infections, or, specifically against empyema, owing to the large amount of vaccine and the prolonged nature of treatment required.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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Pellagra Incidence in Relation to Sex, Age, Season, Occupation and "Disabling Sickness" in Seven Cotton Mill Villages of South Carolina during 1916.—GOLDBERGER, WHEELER and SYDENSTRICKER (*Public Health Reports*, No. 28, xxxv, 1650) conclude their study by the following summary: "(1) During 1916 the incidence of pellagra among the members of the families of white mill operatives of seven representative cotton mill villages of South Carolina was included in our study. (2) In a population of 4399 a total of 115 definite cases, representing a rate of 26.1 per 1000, was recorded. If 73 cases with ill-defined eruption recorded as 'suspects' are included, there were in all 188 cases and an incidence rate of fully 42.7 per 1000 in this population. (3) The data appear to indicate that the disease is rare in children at the age of two and under; that among both males and females up to twenty years the incidence is similar, being higher among children between two and ten years than in persons of the ages of ten to nineteen inclusive; and that among adults twenty to fifty-four years old the incidence is many times higher in females than in males. (4) There was a sharp rise in incidence during April and May, reaching a well-defined peak in June. The season of onset appeared to be confined almost entirely to the six months April to September inclusive. (5) The pellagra rate among both males and females was considerably higher for the non-millworkers than for the millworkers. (6) While

the pellagra rate among non-millworking females was approximately four times as high as that among millworking females, the rate for disabling sickness appeared distinctly higher in millworking than in non-millworking females. The disability indicated by the higher sickness rate among millworking females appeared not to influence materially the pellagra rate in this group."

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**A Study of the Relation of Factors of a Sanitary Character to Pellagra Incidence in Seven Cotton Mill Villages of South Carolina in 1916.**—GOLDBERGER, WHEELER and SYDENSTRICKER (*Public Health Reports*, 1920, No. 29, xxxv, 1701) conclude the study of their problem as follows: "This study of the relation of factors of sanitary importance to the incidence of pellagra in seven representative mill villages has failed to reveal any consistent correlation between them. Although based on a rather small mass of data and, in itself, not warranting any conclusions, it may, nevertheless, be noted as not without significance that this result, at any rate, affords no support for the view until recently, at least, quite widely entertained in this country, that pellagra is 'an intestinal infection transmitted in much the same way as typhoid fever;' nor does the evidence adduced in favor of this view by other workers, when rightly considered, afford it any real support. It may be of interest to add that the results of the very much more extensive study of this subject carried on by us during 1917 and 1918, to be presented in a later communication, are in harmony with and confirm those here recorded."

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**Absorption of Cyanide Gas by Foodstuffs.**—The Public Health Service (*Public Health Reports*, No. 27, xxxv, 1597) has had a series of experiments made to determine whether there is any danger of poisoning from the use of foodstuffs that have been exposed to cyanide gas in the process of fumigation for the destruction of vermin. The experiments were conducted by exposing bread and milk to the gas and then feeding the exposed food to mice, and, as a result of the tests, it was considered that the danger was "exceedingly remote."

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**Can the Mosquito Convey Infection from a Malaria Patient Undergoing Treatment? Does Sporogony Affect Mosquito Life?**—MAYNE (*Public Health Reports*, No. 28, xxxv, 1664) reviews the evidence on this subject, which indicates that the gametocytes taken with the blood of a patient undergoing quinin treatment develop in the usual manner and that transmission to a new human host may occur. The infestation of the mosquito host does not appear to be prejudicial to the life of the insect; this is in contrast with the high mortality of mosquitoes infested with microfilarial parasites.

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**Utility of Antiplague Vaccines and Serums.**—McCoy and CHAPIN (*Public Health Reports*, No. 28, xxxv, 1647) review the evidence of the value of biologic products in the prophylaxis and treatment of plague. The work of Haffkine and others is reviewed and the opinion is expressed that while vaccine is probably of some value it is not capable of controlling an outbreak of plague. The evidence on the prophylactic value of serum is not conclusive and the agent need not be seriously con-

sidered in this connection. The therapeutic use of serum is usually advantageous but brilliant results are seldom seen. The concluding paragraph of the paper is as follows: "It seems rather unfortunate to those who are called on for advice in connection with a plague outbreak to find that popular and professional interest is so frequently centered on the subject of prophylaxis by vaccines or serums and on treatment by serum when, in fact, the situation demands active measures against rodents. Under American conditions at least it is not a matter of much importance whether biological products are used in a prophylactic way or not. The health officer need give but little consideration to them in his plans to deal with an outbreak of bubonic plague. If people want to be vaccinated for prophylactic purposes there is no objection to complying, but the community should not be allowed to delude itself into the belief that plague may be controlled in this manner. The essential features of an antiplague campaign should be the extermination of rodents and not immunization by means of vaccines or serums."

**Treatment of Leprosy, with Especial Reference to Some New Chaulmoogra Oil Derivatives.**—McDONALD and DEAN (*Public Health Reports* No. 34, xxxv, 1959) take a most optimistic view of the prospects of cure in the treatment of leprosy by means of the ethyl esters of the fatty acids found in chaulmoogra oil. Their conclusions are as follows: (1) The intramuscular injection of the ethyl esters of the fatty acids of chaulmoogra oil usually leads to a rapid improvement in the clinical symptoms of leprosy. In many cases the lesions disappear, except for scars and permanent injuries, and the leprosy bacillus can no longer be demonstrated. (2) When combined with iodine, the fatty acids of chaulmoogra oil and their esters give good results; but there is no adequate experimental proof that this addition of iodine causes any increase in the effectiveness of the materials used. (3) All of the available evidence obtained from the use of fractions of the fatty acids of chaulmoogra oil indicates that the therapeutic action is due to one or more of the fatty acids of the oil or to some as yet unidentified substance associated therewith. The various methods of fractionation heretofore employed have failed to demonstrate the active agent. (4) Although conclusive evidence is not at hand, it is probable that the oral administration of chaulmoogra oil derivatives is of minor importance compared with the injections. (5) In treating leprosy, it is important to make use of all auxiliary agencies to build up and maintain bodily vigor. (6) Hypodermic injections of the ethyl esters into leprosy nodules are followed by marked swelling with ultimate recession of the lesions. This is a valuable auxiliary treatment for especially resistant lesions.

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ORIGINAL ARTICLES.

SOME NEWER CONCEPTS IN DIGITALIS THERAPY.\*

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Not quite twelve years ago Mackenzie published his epoch-making work on *Diseases of the Heart*, which marked the beginning of a revolution in our knowledge of the physiology and pathology of that important organ. At about the same time Einthoven brought forth his string galvanometer as a clinical instrument for the scientific study of the mechanism of the heart-beat; and through the work of Mackenzie the polygraph had become an instrument of great clinical value. We were thus, all at once, provided with a new outlook upon the functions of the heart in health and disease and with instruments of precision for the study of these functions. During this brief span of years our knowledge of the heart's normal and pathologic physiology has been advanced far more than it had in the preceding century, and with this advance there came the opportunity for the more accurate investigation of the action of drugs upon the heart in man. Many such investigations have been made with reference to the actions of digitalis and the digitalis bodies, and it is with the results of some of these that the present paper is concerned.

Slowing of the heart has been regarded as one of the characteristic actions of digitalis in man ever since it was first observed by Withering. The most superficial observation should have revealed

\* Read before the College of Physicians of Philadelphia, April 7, 1920.  
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that this action often fails to appear even when the administration of digitalis is followed by beneficial effects. We now know that the only large group of cases in which digitalis produces marked reduction in the heart-rate is that of auricular fibrillation. With but two exceptions the therapeutic administration of digitalis is seldom followed by a significant degree of slowing of the heart-rate in the presence of the normal sinus rhythm. The two exceptions are those cases of heart-failure in which marked edema is present and those with hypodynamic, unstable hearts in which the rate is generally rapid but is subject to spontaneous fluctuations. In both of these digitalis generally produces considerable slowing. Finally, slowing of the heart is seen in man not infrequently as one of the common manifestations of digitalis intoxication, when it is due to the production of some degree of heart-block. When the normal sinus rhythm is present, therefore, slowing cannot be regarded as one of the primary characteristic therapeutic actions of digitalis. The recognition of this fact is of considerable therapeutic importance, for it reveals the fallacy of one of the chief objections advanced against the administration of digitalis in cases of heart failure due to aortic insufficiency, and recent clinical experience has shown that digitalis is not only not contra-indicated in such cases but is often of great value for the relief of the failure. It should be said, however, in this connection that heart-failure does not usually result from aortic insufficiency until a late stage, when the contractile power of the ventricular musculature has been greatly exhausted. Therefore, while digitalis is not contra-indicated its administration not infrequently fails to relieve the heart-failure. There is no satisfactory evidence, however, that its judicious employment is ever harmful in such cases, and it should always be given a trial.

The mechanism by which digitalis produces slowing of the heart has been the subject of recent investigation, especially by Cushny, Marris and Silberberg,<sup>1</sup> Cushny<sup>2</sup> and others. It has long been known, as demonstrated in animal experiments, that digitalis stimulates the vagus center in the medulla and thereby reduces the rate of the heart in one of two ways: Either the rate of the whole heart is diminished by depression of the rate of impulse formation in the sinus or the rate of the ventricles alone is reduced through depression of auriculoventricular conduction to a degree sufficient to cause partial or complete heart-block. The former, slowing of the whole heart, is the type commonly found in patients presenting the normal sinus rhythm—that is, in patients with the hypodynamic heart and in those with edema. The latter, as has been mentioned, is commonly a manifestation of minor intoxication by digitalis, and also occurs chiefly in hearts with the normal rhythm.

<sup>1</sup> Action of Digitalis in Therapeutics, Heart, 1912-13, iv, 33.

<sup>2</sup> Digitalis in Auricular Fibrillation, Jour. Pharm. and Exp. Therap., 1918, ii, 103.

It has been said that digitalis is contra-indicated in cases of partial heart-block, and in those in which there is evidence of impaired conduction, as shown by prolongation of the *A-V* or *P-R* intervals. It has also been stated that marked prolongation of conduction time and partial heart-block occur in man from the use of digitalis only in cases previously showing some impairment of conduction. Neither of these contentions is wholly correct. Extensive clinical observations have shown conclusively that while there is an increased tendency for digitalis to enhance a preëxisting depression of conduction or partial block it is by no means contra-indicated in cases of this type. In many such cases it may be administered with satisfactory results without further prolongation of conduction time or increase in heart-block. In others the block, or impaired conduction, seems to be largely secondary to the existence of the heart-failure, and when digitalis relieves the failure the block may disappear or the conduction time may be shortened. Finally, if the administration of digitalis does show a tendency to increase an existing impairment of conduction this can generally be overcome by the administration of suitable doses of atropin to depress the cardiac endings of the vagus and thereby remove the effects of the central stimulation. While digitalis is not contra-indicated in cases with impaired conduction it should always be administered with caution and the patient should be observed at frequent intervals, always with the aid of instrumental methods if possible, to detect at once any increased depression of conduction should it develop.

The belief that therapeutic doses of digitalis do not frequently depress conduction in man unless there is an existent impairment of this function has been overthrown by Cohn<sup>3</sup> and by White and Sattler,<sup>4</sup> who have shown that some delay in conduction time is an almost invariable phenomenon of digitalis action even in normal persons. It is true, however, that the depression is not usually very marked until the stage of minor digitalis intoxication is reached. The prolongation of conduction time may progress gradually during the administration of digitalis or it may develop suddenly. It seems quite probable that the delayed conduction may constitute an action of digitalis which is of some therapeutic value in cases in which the rate of the heart is not altered even though the delay be small. The interval between the auricular and the ventricular contractions is increased by the time by which conduction is prolonged, and even when this does not exceed 0.02 of a second it means a considerable increase in the time allowed for the auricles to empty into the ventricles. This should be quite sufficient to increase

<sup>3</sup> Clinical and Electrocardiographic Studies on the Action of Digitalis, *Jour. Am. Med. Assn.*, 1915, lxx, 1527.

<sup>4</sup> Effect of Digitalis on the Normal Human Electrocardiogram, with Especial Reference to *A-V* Conduction, *Jour. Exp. Med.*, 1916, xxiii, 613.

materially the amount of blood flowing into the ventricle, especially in cases of mitral stenosis, and thereby improve the circulation.

Recognition of the capacity of digitalis to depress auriculoventricular conduction through stimulation of the vagus center and the discovery of the fact that its striking capacity to slow the ventricular rate in auricular fibrillation is due to the blocking off from the ventricles of many of the feebler auricular impulses, led to the tacit assumption that this block was also dependent upon central vagus stimulation. Cushny and his associates, however, observed that the block produced in auricular fibrillation, unlike that in the regular heart, could not in many cases be abolished by depression of the vagus endings in the heart by atropin. That is, they found that before digitalis was given the administration of atropin produced a greater acceleration in ventricular rate than followed the same dose when given after the ventricles had been slowed by digitalis. They thereupon investigated the mechanism of the slowing produced by digitalis in man, in intact animals and in perfused, isolated animals' hearts, and concluded there are two types of mechanism by which this is accomplished. Type A is purely inhibitory through central vagal stimulation; it can be antagonized by paralysis of the vagus endings with atropin; and it is the mechanism commonly found in the presence of the normal sinus rhythm. Type B is the result of a direct action of digitalis on the conducting tissues to depress their functions; it is unaffected by atropin; and it is the mechanism involved in most cases of auricular fibrillation and in rare instances when the rhythm is normal. It occurs typically in animal hearts which have become malnourished by long perfusion, and Cushny suggests that it rests largely upon the existence of malnutrition. He believes that it is common in auricular fibrillation because that condition especially favors the development of malnutrition of the human heart.

The accuracy of Cushny's observations is not to be doubted, but we believe that his conclusions are too sweeping. In the first place Cushny's own observations do not seem to exclude all participation of the vagus inhibitory action, for while he shows that the administration of atropin produces a greater acceleration in ventricular rate, both actual and proportional, when the heart is not slowed by digitalis than when it is, his records also show that atropin does accelerate the rate even when it has been greatly slowed by digitalis. This seems to indicate the existence of some vagal inhibition, and his arguments to the contrary are not altogether convincing. Further, his contention that the slowing is produced by a direct action of digitalis upon the junctional conducting tissues does not seem to have been proved by his experiments, although the action is evidently upon some structure distal to the vagal endings. Cohn

and Fraser<sup>5</sup> have shown that even when the administration of atropin fails to restore the heart-rate to its previous level after it has been slowed by digitalis the atropin, nevertheless, always removes completely whatever delay in conduction the digitalis may have produced. The whole matter is in need of further investigation.

So much for the mechanism by which digitalis slows the human heart, let us now briefly consider the therapeutic value of reducing the rate of the ventricles or of the whole heart. We have already indicated how simple prolongation of conduction time may be of value in mitral stenosis. Reduction in the rate of the heart, or that of its ventricles, is accompanied by a lengthening of the diastolic or resting-phase of the ventricles, while the duration of the systolic-phase is but little altered. This lengthening of diastole allows a larger volume of blood to flow into the ventricles and gives time for a more complete recovery of their contractile power. The force and volume output of ventricular systole are thus increased, and since more blood is thrown into the aorta and diastole is prolonged, coronary circulation is increased, the nutrition of the ventricular musculature is improved and internal respiration is more perfect in the ventricles. These secondary results are especially pronounced in cases of auricular fibrillation because of the added fact of the elimination of the frequent abortive ventricular contractions which exhaust the contractile power and do not contribute materially to the nutrition of the ventricular musculature. It should be mentioned in this connection that while digitalis so effectively slows the ventricles in auricular fibrillation the rate and the fibrillation of the auricles are not altered.

While slowing alone can account for all of those beneficial effects of digitalis in man which lead to the restoration of the failing heart and secondarily to the disappearance of the patient's symptoms, it is far from being a constant effect. The contention that the beneficial effects of the administration of digitalis are wholly attributable to its capacity to slow the heart is not supported by the facts, for there are many cases in which digitalis is quite effective in restoring the failing heart, although it does not alter its rate. The experiments of Gottlieb and Magnus<sup>6</sup> and others, on the isolated perfused heart, demonstrate that digitalis is capable of producing a marked increase in the volume output of the ventricles per beat, both by increasing the extent of diastolic filling and the completeness of systolic emptying. They also show that the force of ventricular systole is markedly increased by digitalis. These actions are necessarily exerted directly upon the ventricular musculature, since they occur in the heart after its removal from the body. Francois-

<sup>5</sup> Certain Effects of Digitalis on the Heart, XVIIth Int. Cong. Med., 1913, Medicine.

<sup>6</sup> Digitalis und Herzarbeit, Arch. f. exp. Path. and Pharm., 1904, li, 30.

Frank observed similar results from the administration of digitalis to living animals. These experiments suggest the existence of a similar direct action of digitalis on the human heart to increase the force and volume of ventricular systole. Although there are no methods available for proving the existence of such an action in man, it seems highly probable that it does occur for the following reasons: In the first place the alterations in the T wave of the electrocardiogram, which Cohn, Fraser and Jamieson<sup>7</sup> have shown to occur commonly early in the course of the administration of digitalis to man, are apparently due to a direct action of the drug upon the myocardium. Cushny's observations previously discussed also seem to prove that digitalis exerts a considerable direct myocardial action in man, and there is every reason to believe that the production of ventricular premature contractions by digitalis is the result of a direct muscular action. There is evidence, therefore, that digitalis does act directly upon the human myocardium. In the second place we know that digitalis is capable of relieving heart-failure and restoring cardiac efficiency in cases in which it produces no slowing, and even in cases of complete heart-block. It is impossible to account satisfactorily for its effects in such cases except by assuming that it increases the force or magnitude, or both, of ventricular systole.

We have seen that digitalis may exert one or more of the following actions in man when administered in therapeutic doses:

1. It may slow the rate of the whole heart through stimulation of the vagus center.
2. It may prolong the time of auriculoventricular conduction through a similar action.
3. It may slow the rate of the ventricles, either by the production of some degree of heart-block through central vagal stimulation or by virtue of some direct action on the heart.
4. It seems probable that it may exert a direct action on the myocardium which results in an increase in the force or magnitude, or both, of ventricular systole.

These, and these alone, seem in the present state of our knowledge to be the primary therapeutic actions of digitalis, but their secondary results are limited only by the conditions existing in the given case of heart-failure. By them the failing heart is restored and the circulation of blood through the body is improved.<sup>8</sup> The blood is more perfectly ventilated in the lungs; stasis and congestion are overcome; dyspnea, orthopnea, cyanosis and cough diminish and finally disappear; edema and transudates are absorbed; diuresis is produced.

<sup>7</sup> Influence of Digitalis on the T-wave of the Human Electrocardiogram, *Jour. Exp. Med.*, 1915, xxi, 593.

<sup>8</sup> Stewart, G. N., and Scott, R. W.: Change Produced in the Bloodflow (in the Hands) under the Influence of Digitalis in Cases of Auricular Fibrillation, *Jour. Pharm. and Exp. Therap.*, 1915, vii, 263.

Before leaving the subject of the clinical pharmacology of digitalis a few matters demand brief discussion because they do not even yet seem to be clearly understood by all. The impression that the existence of a high systolic blood-pressure in a patient with heart-failure contra-indicates the administration of digitalis seems still to linger in the minds of many. The subject of the influence of digitalis on the blood-pressure in man was discussed a few years ago,<sup>9</sup> and it was shown that the vasoconstriction which could be demonstrated to occur in animals and in isolated surviving vessels under the influence of digitalis took place only when amounts of the drug were used which were far in excess of any which could possibly be given to man. It was shown that there is no evidence that either digitalis or digitoxin has any direct action on the bloodvessels when given to man even in large therapeutic doses. A large number of careful observations of the effects of the administration upon the blood-pressure in man were analyzed and it was found that the changes in the systolic and diastolic pressures are generally relatively slight, the tendency being for the pressures to be altered in the direction of the normal. There is a marked tendency for the pulse-pressure—the difference between the systolic and diastolic pressures—to increase under the influence of digitalis, chiefly through reduction of the diastolic pressure, in cases of heart-failure in which the failure is relieved. A decided fall in the systolic pressure is to be anticipated when digitalis relieves heart-failure in cases in which it is accompanied by a high systolic pressure and marked edema. There is also a marked tendency for digitalis to reduce the systolic pressure from its high level in cases with marked dyspnea, cyanosis and circulatory stasis. All of the facts, therefore, show conclusively that digitalis is not contra-indicated by the existence of high blood-pressure.

A closely related matter is that of the possible action of digitalis on the human coronary arteries. Of course, it is not feasible to detect such an action with certainty in man, yet some recent textbooks state that, in toxic doses at least, digitalis may produce a dangerous constriction of the coronaries, and it has also been argued that when pulsus alternans is produced or aggravated by digitalis the phenomenon is due to coronary constriction. These beliefs have also been responsible for the view that digitalis is contra-indicated in cases with so-called angina pectoris. We are convinced that these ideas are misleading and erroneous: (1) The painstaking animal experiments of Felix Meyer<sup>10</sup> and of Sakai and Saneyoshi<sup>11</sup>

<sup>9</sup> Eggleston, Cary: Influence of Large Doses of Digitalis and Digitoxin on the Blood-pressure in Man, Jour. Am. Med. Assn., 1917, lxix, 951.

<sup>10</sup> Ueber die Wirkung verschiedener Arzneimittel auf die Coronargefäesse des lebenden Tieres. Arch. f. Anat. and Phys., phys. Abteil., 1912, 223.

<sup>11</sup> Ueber die Wirkung einiger Herzmittel auf die Koronargefäesse, Arch. exp. Path. and Pharm., 1914-15, lxxviii, 331.

and others have shown that the digitalis bodies do not constrict the coronaries of the heart *in situ*. In fact, digitalis seems to dilate them actively while strophanthin increases the coronary blood flow indirectly by elevation of the aortic pressure. (2) The statement that marked coronary constriction may occur in man from toxic doses of digitalis is based upon pure assumption and not upon any satisfactory evidence. (3) The occurrence or aggravation of pulsus alternans occasionally seen in cases of advanced heart failure under digitalis treatment does not prove that the drug is responsible for the change or that coronary constriction is present. Pulsus alternans may well develop spontaneously in such cases and in spite of the administration of digitalis rather than because of it. When alternans is already present it is strong evidence that the exhaustion of the heart is almost complete, and in such a heart the exhaustion may progress even when digitalis is being used in adequate doses for all forms of treatment frequently fail to check the progress of failure in such late stages of heart disease. (4) Digitalis is often of great value in cases with pulsus alternans and not infrequently restores the normal rhythm, at least temporarily.<sup>12</sup> (5) When the administration of digitalis results in the relief of heart-failure and the restoration of cardiac efficiency it is inconceivable that it should improve the capacity of the heart for work and at the same time reduce and impair its nutrition and internal respiration by a constriction of the coronaries. It is a fact also that anginal pain is usually but a symptom of heart-failure and the control of the failure by the administration of digitalis frequently relieves the pain. In such cases the continued or intermittent use of digitalis, by preventing the recurrence of failure, often also prevents the recurrence of the pain.

The third question upon which some doubt seems to persist is that of the mechanism of the diuretic action of digitalis. While it has been claimed that digitalis exerts a specific diuretic action on the kidneys, or that it produces diuresis by selective vasodilatation of the renal arterioles, the evidence for these claims is quite unsatisfactory, and careful studies have shown conclusively that the drug is not a diuretic in normal animals. It has also been observed repeatedly that no diuresis follows the administration of digitalis to normal human beings or to those with heart-failure uncomplicated with edema or serous effusions. In cases of nephritis with edema, or even with general anasarca, digitalis also produces no diuresis when heart-failure is not associated with the nephritis. When, however, heart-failure is accompanied with edema or anasarca profuse diuresis may follow the administration of digitalis, but this is found to occur only when the heart-failure is more or less effectively

<sup>12</sup> Windle, J. D.: Clinical Observations on the Effect of Digitalis in Heart Disease with Pulsus Alternans, *Quart. Jour. Med.*, 1916-17, x, 274.

overcome by the drug, and when the heart failure is not affected no diuresis ensues from its administration. It is clear, then, that the diuretic action of digitalis in man is essentially secondary to its capacity to relieve heart-failure and restore the circulation; and when it is effective in edematous cases of heart-failure, it is often one of the earliest of the manifestations of the action of the drug, though other evidences can be detected if looked for. When adequate digitalization fails to produce diuresis in a patient with edema and heart-failure it will almost invariably be found that either the heart-failure has not been relieved or that the failure is complicated by nephritis, which then demands appropriate treatment.

Having reviewed some of the more important therapeutic actions of digitalis, let us now turn to the consideration of certain of the problems connected with its oral administration to man. In approaching these questions we must bear in mind the following points:

1. The indication for the administration of digitalis is determined by the degree of heart-failure, not by the cause of the failure.
2. The dosage and the criteria of the action of digitalis are identical, irrespective of the cause of the heart-failure, although the method of administration may be influenced by the cause of the failure.
3. In the absence of satisfactory therapeutic response one can be certain that digitalis has been given a fair trial only when it has been administered to the point of production of one or more of the criteria of minor intoxication.

The proper administration of digitalis demands the ability to judge the degree of digitalization which is being produced because all of the digitalis bodies can cause serious poisoning and because the nature of heart-failure is such that incomplete recovery or death may result from inadequate treatment. The following are the more important criteria by which the degree of digitalization can be judged:

In cases which respond favorably there is a group of phenomena, both subjective and objective, which indicate more or less effective digitalization and which may be embraced by the term, "Clinical Improvement." These include all such definite evidences of improvement in the circulation as relief or disappearance of the patient's respiratory symptoms; relief of cardiac or precordial pain; disappearance of the nausea due to splanchnic congestion; the production of diuresis; diminution or disappearance of evidences of congestion of the liver; fall in pulse-rate; decreased degree of irregularity in auricular fibrillation together with reduction in the pulse deficit, or its disappearance.

The number and nature of these phenomena and the extent



of their development depend on the conditions existing prior to treatment, on the capacity of the heart to respond to digitalis and on the adequacy of treatment. When well-developed they usually indicate adequate digitalization and the discontinuance of the drug or a reduction in its dose. Their occurrence also corresponds in the majority of cases to the appearance of minor toxic actions of digitalis.

The following phenomena occur independently of a therapeutic response and are not necessarily indicative of a toxic action of digitalis, though each is certain evidence of the absorption and action of the drug: Prolongation of the time of auriculoventricular conduction, which can be detected in graphic records as one of the earliest and most constant effects of digitalis upon the heart; flattening or inversion of the *T* wave of the electrocardiogram, which is nearly as constant as the preceding but does not occur quite so early; the production of sinus arrhythmia or the exaggeration of a preëxisting sinus arrhythmia.

Finally, the following phenomena are indicative of some degree of digitalis intoxication and their appearance demands the cessation of further administration or a sharp reduction in the dose: Nausea or vomiting; marked grade of sinus arrhythmia, especially when phasic in type and independent of respiration; partial or complete heart-block; premature contractions; the "coupled rhythm" due to the regular recurrence of a premature contraction after each regular beat; auriculoventricular dissociation; the *A-V* or nodal rhythm; ventricular tachycardia; other rare disturbances of the cardiac rhythm. Two or more of these phenomena not infrequently occur together in the same patient.

These arrhythmias of digitalis intoxication must be distinguished from those due to the heart-failure itself. This can frequently be accomplished only as the result of the most careful and constant observation of the patient from the outset, usually with the aid of graphic records, for it is impossible to distinguish without knowledge of the previous condition whether block, premature contractions, etc., are due to digitalis or to the progress of the heart-failure. In cases of advanced heart-failure in which the administration of digitalis must always be carried to the limits of the patient's tolerance when the desired therapeutic effects are not obtained, the knowledge and skill of the clinician are frequently taxed to the limit to determine when to stop the administration of the drug. In all such cases it is best to secure the aid of a specialist, preferably from the beginning, but always before it is too late for his services to be of value.

While it is generally desirable in the treatment of heart-failure to secure the maximal therapeutic effects of digitalis promptly the urgency of the symptoms and various other factors must determine the rapidity with which digitalization should be induced in any

given patient. With this in mind, and in view of the facts already set forth, three general plans of dosage by oral administration are suggested.

**Small Dose Method.** From four to six days are generally required for digitalization by this method;  $\frac{1}{8}$  to  $\frac{1}{4}$  gram (gr. ij to gr. iv) of the powdered leaf or  $1\frac{1}{4}$  to  $2\frac{1}{2}$  c.c. (m xx to m xl) of the tincture should be administered every four hours—four doses daily—and continued until digitalization is induced. With weak or poorly absorbed specimens of digitalis full digitalization may not be secured at all by this method or it may require ten days or more to secure it.

**Large Dose Method.** From one to two days are required for digitalization. During the first twenty-four hours a dose of  $\frac{4}{10}$  gram (gr. vj to gr. vii) of the powdered leaf or 4 c.c. (dram j) of the tincture should be administered every six hours, day and night, for four doses. On the second day the dose should be reduced one-half and the interval may be shortened to four hours, giving four doses per day and none at night. This latter dose and interval should be continued until full digitalization is secured.

**The Body Weight Method.** This method permits full digitalization within ten to twenty hours from the beginning of administration and is specially serviceable in cases manifesting urgent symptoms. Its use has proved so satisfactory during the five years that have elapsed since its introduction that it has been possible very largely to do away with the necessity for the intravenous or intramuscular administration of ouabain, strophanthin or other digitalis preparation. It has been described in detail so recently that it is sufficient to refer to some of the published papers in which it is discussed.<sup>13 14 15 16</sup>

Mention of other members of the digitalis group of drugs has been omitted in discussing dosage by oral administration, because digitalis itself is preëminently the drug of choice by reason of its availability, absorbability and persistence of action. Its availability needs no comment but a few remarks are in place with reference to the choice of preparation. The preparation selected should always be one which has been assayed biologically and proved to be of high activity. It should be remembered, however, that the biologic unit is a more or less arbitrary figure which merely serves to indicate the relative activity of the preparation, as determined by a particular method of assay, and in general it bears no direct relation to the dose

<sup>13</sup> Eggleston, Cary: Digitalis Dosage, Arch. Int. Med., 1916, xvi, 1.

<sup>14</sup> White, S. M., and Morris, R. E.: Eggleston Method of Administering Digitalis, Arch. Int. Med., 1918, xxi, 740.

<sup>15</sup> Robinson, G. C.: Rapidity and Persistence of the Action of Digitalis on Hearts showing Auricular Fibrillation, AM. JOUR. MED. SC., 1920, cliv, 121.

<sup>16</sup> Eggleston, Cary: Administration of Digitalis by the "Eggleston Method," Jour. Am. Med. Assn., 1920, lxxiv, 733.

of the preparation for man. The cat unit, however, is employed for the calculation of the human dose in the Body Weight method of administration. The figures obtained by different methods of bio-assay are not comparable one with another, but it is generally true that a preparation which is highly active, as shown by one method, will be found active by any other, although the activity of a given specimen may differ considerably by different methods of assay.

The particular official form of digitalis selected will depend largely upon the personal preference of the physician, but we are convinced that the powdered leaf and the tincture are the most satisfactory. The dose of each is of convenient bulk; each can be assayed biologically and each keeps for long periods of time without material loss of activity. The powdered leaf is especially to be commended because it can be dispensed in capsules, which are easily carried and pleasant to take, and the disagreeable bitter taste of the fluid preparations is avoided. The dose of the fluidextract is too small for convenience, while that of the infusion is unnecessarily large, in view of its unpleasant flavor. Further the fluidextract is seldom up to standard in activity and the infusion is not assayed. Even when the infusion is prepared from the assayed leaf the activity of different lots is seldom uniform on account of variations in the completeness of extraction of the active constituents.

Of the many proprietary preparations and specialties which are offered with high claims for oral administration none is superior to the powdered leaf or tincture of high grade, and most are decidedly inferior. All are quite costly and the price of some is exorbitant. If one feels impelled to employ one of these, digipuratum or digipoten will be found to be the best, but these are merely carefully assayed, purified preparations from good digitalis leaves.

The materia medica of the digitalis group of drugs is large, but digitalis alone is well absorbed from the alimentary tract of man. *Strophanthus*, *convallaria*, squills, etc., are both poorly and irregularly absorbed. *Strophanthus* deserves special mention, because it is 100 times as active as digitalis, yet the official dose is only half that of digitalis, and it is often given in equal doses. The irregularity of its absorption is of greater importance than the fact that its absorption is generally poor, for in some cases serious poisoning has resulted from the rapid absorption of the customary dose.<sup>17</sup> We are convinced that *strophanthus* should never be used for oral administration to man on account of the danger of serious accident, despite the fact that it often has been so used with satisfactory results.

The subjects of absorption, persistence of action and elimination of digitalis are so closely related that we will discuss them together

<sup>17</sup> Hatcher, R. A., and Bailey H. C.: Clinical Use of *Strophanthus*, Jour. Am. Med. Assn., 1910, iv, 1697.

in the closing section of this discourse. While digitalis is generally well-absorbed from the human alimentary canal, several instances have come to our attention in which absorption was very unsatisfactory.<sup>18</sup> In some instances the poor absorption is unquestionably due to some individual peculiarity on the part of the patient or to some factor in his condition. In others, however, the fault seems to lie with the digitalis, and my colleague, Dr. Robert A. Hatcher, has been able to throw some light on this matter. His work has not yet been published and is still incomplete, but the following observations seem highly significant: Digitalis can be readily separated into two fractions by extraction of its aqueous solution with chloroform. The chloroform-soluble fraction is readily absorbed from the alimentary tract of the cat, while the chloroform-insoluble fraction is poorly and irregularly absorbed. Both fractions are active when injected intravenously, manifesting the typical actions of digitalis. The two fractions vary widely in the relative proportions in which they are present in different samples of digitalis, and at least one of the samples of digitalis which showed very poor absorption in man contained relatively very little of the chloroform-soluble, absorbable fraction.

Dr. Hatcher has supplied me with solutions of these two fractions, of equal activity by the cat test, and these have been administered to a number of patients to observe their absorption. These observations, too, are incomplete, but they have shown quite definitely that the chloroform-soluble fraction is well absorbed from the human alimentary tract while the chloroform-insoluble fraction is absorbed poorly. Comparing the amounts required to produce minor intoxication or full therapeutic effects, nearly four times as much of the chloroform-insoluble fraction as of the chloroform-soluble is required to produce similar effects. This is true even when the two fractions are given on different occasions to the same patient. The rate of absorption of the chloroform-soluble fraction seems to be quite equal to that of the best digitalis, but we do not yet know that it is any more rapid. The results of these observations will be reported in detail at a later time.<sup>19</sup>

It has been shown that digitalis of high grade is generally well absorbed from the digestive tract of man, and it seems apparent that the absorption of a single dose is completed within six hours. Recently, Pardee (unpublished) has shown that there is definite electrocardiographic evidence of considerable absorption in from two to four hours, and the observations of Levy (unpublished) and

<sup>18</sup> Wedd, A. M.: Observations on the Clinical Pharmacology of Digitalis, *Bull. Johns Hopkins Hosp.*, 1919, xxx, 131.

<sup>19</sup> Since this was written two preliminary papers have appeared on this work: Hatcher, Robert A., Some Observations on the Pharmacology of a Digitalis Body, *Jour. Am. Med. Assn.*, 1920, lxxv, 460. Eggleston, Cary, The Absorption of a Digitalis Body, *Jour. Am. Med. Assn.*, 1920, lxxv, 463.

of Robinson<sup>20</sup> confirm this. These observations are quite at variance with the rather general belief that digitalis is slowly absorbed. That belief seems to have been based on the older mistaken idea that from three to six days were always required to secure digitalization in man, which, in turn, arose from the administration of single doses which were too small. We know now that digitalis is fairly rapidly absorbed and that full digitalization can be secured by oral administration certainly within twenty-four hours after the first dose, and frequently within ten hours.

Through the work of Hatcher<sup>21</sup> on animals and of Eggleston,<sup>22</sup> Cohn and his associates, Robinson and others, on man, it has been proved that the action of digitalis on the human heart may persist for periods up to two weeks or longer after administration has been stopped. This persistence of action is one of the valuable features of digitalis as a cardiac remedy and its recognition is of considerable therapeutic importance. In the first place it accounts for the phenomenon previously called "cumulation," and always somewhat shrouded in mystery. Taken together with the knowledge of the rate of absorption of digitalis, and of its average dose for man, it demonstrates the fact that it is quite unnecessary to administer digitalis at the short intervals customarily observed. It is never necessary to administer a dose more often than every four hours, and a six-hour interval is generally preferable. Further, when a patient is to be kept upon the continuous administration of a small dose of digitalis this need be taken only once daily instead of being divided into two or three doses. Finally, the persistence of action must always be kept in mind when one considers the administration of ouabain (crystalline strophanthin) or amorphous strophanthin intravenously or intramuscularly, for the doses of the latter are commonly large, in terms of activity, and serious or fatal poisoning has occurred from such injections in patients who have recently been receiving digitalis.

The mechanism of this persistent action is not definitely understood, but the evidence seems to indicate that it is due to the firm fixation of a small amount of the drug in the tissues of the heart where it continues to exert its actions. One of the strongest reasons for believing this to be the case is the fact that digitalis disappears from the blood stream very rapidly after intravenous injection in a variety of animals. Some earlier pharmacologic experiments also seem to indicate that the heart is capable of storing minute quantities of the digitalis bodies.

Very recently Pardee<sup>23</sup> has studied the rate of the elimination

<sup>20</sup> Loc. cit.

<sup>21</sup> Persistence of the Action of the Digitalins, *Arch. Int. Med.*, 1912, x, 268.

<sup>22</sup> Clinical Observations on the Duration of Digitalis Action, *Jour. Am. Med. Assn.*, 1912, lix, 1352.

<sup>23</sup> Notes on Digitalis Medication, *Jour. Am. Med. Assn.*, 1919, lxxiii, 1822.

of digitalis in man by administering the drug orally until a definite effect was produced and determining the dose required. After a lapse of an interval during which no digitalis was administered the same preparation was again given and the amount determined which was required to reinduce the effect previously produced. In this way, using a single sample of tincture of digitalis, he determined that the rate of elimination amounted to about twenty-two minims per day. This figure, of course, applies only to the particular specimen of digitalis with which he worked, but it is significant and agrees with the general impression that from  $1\frac{1}{2}$  to 2 grains of digitalis (15 to 20 minims of the tincture) can generally be administered over long periods of time to prevent the recurrence of heart-failure, and without producing intoxication.

Finally, in closing, let me refer briefly to the investigations of Hatcher and Eggleston<sup>24</sup> on the elimination of certain digitalis bodies from the animal organism, since they throw some light on the mechanism by which elimination is accomplished. Their investigations show that in animals at least both the liver and the kidneys participate. The liver seems to be capable of rapidly fixing, and probably also of destroying or decomposing, a large proportion of ouabain after its entrance into the blood stream. Other tissues in the body also apparently can fix rapidly and thereby remove from the blood stream large amounts of ouabain, but the liver seems to be the organ chiefly concerned in the elimination. The part played by the kidneys is normally relatively insignificant. Whether or not these are the mechanisms involved in man is not known, and at the present time there seems to be no method of attacking the problem in the human being.

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## ROENTGENOLOGICAL ASPECTS OF LOWER RIGHT QUADRANT LESIONS.<sup>1</sup>

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THE diagnosis of lower right quadrant lesions is a matter of great importance; not only is this because of the frequent occurrence of appendicitis, but because of other lesions which are apt to present

<sup>24</sup> Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, *Jour. Pharm. and Exp. Therap.*, 1919, xii, 405.

<sup>1</sup> Read at the meeting of the American Gastro-enterological Association, Atlantic City, May 3, 1920.

themselves in this region, the differential diagnosis of which is often fraught with much difficulty.

Among the affections most frequently observed in the lower right quadrant of the abdomen may be mentioned:

1. Appendicitis.
2. Incompetent ileocecal valve and ileal stasis.
3. Dilatation of the cecum with retention.
4. Adhesions and angulations.
5. Ulcerations due to tuberculosis.
6. Ulcerations due to carcinoma.

In the roentgen-ray study of lower right quadrant lesions both bismuth meals and bismuth enemata must be employed. When the bismuth meal is taken it ordinarily reaches the cecum in five to eight hours, according to the character of the meal, and the transverse colon in twelve hours. Delay in the passage of the bismuth may be due to a dilatation of the cecum, to ptosis or to adhesions, to ileal stasis and angulation; ulcerations or carcinoma. The bismuth enemata supplement the information obtained by the meal. These consist of 5 ounces of bismuth subcarbonate to the liter of water, to which sufficient mucilage of acacia is added to suspend the bismuth. The patient is placed in the knee-chest position, and the low enema is allowed to run in slowly by gravity. This method of examination is especially useful not only in determining lesions of the lower bowel but also of the lower right quadrant.

1. *Appendicitis. Acute Appendicitis.* Pfahler has called attention to the diagnostic value of the roentgen ray in acute appendicitis in certain instances, in that in those cases in which symptoms of acute appendicitis appear, due to beginning pneumonia in the lower right lobe, the lesion can be demonstrated in the lung, thus differentiating pneumonia from appendicitis, and that by filling the colon and thus determining the area of acute tenderness acute appendicitis may be differentiated from other acute lesions in the lower right quadrant.

*Chronic Appendicitis.* A roentgen-ray examination of the appendix itself in its chronic state is capable of rendering valuable service in many instances. This, of course, only applies to those cases in which the lumen is patent, while in the very chronic forms the lumen of the appendix may be completely closed as a result of an obliterative process and consequently the bismuth will fail to enter and the appendix naturally cannot be visualized. Case recommends a special technic for the examination of the appendix, and emphasizes two points: (1) The necessity of examining the patient in a horizontal position, with the screen over the abdomen and the tube underneath the table; (2) the necessity of palpating the abdomen under the screen with the gloved finger or preferably with a wooden spoon and noting the localized tenderness. The time of the examination is of some importance. In six hours usually the

cecum is fairly filled, and at that time the appendix under palpation will also probably fill. From this time on until the bowels are empty and frequently for some time afterward the appendix remains visible. The ordinary technic will frequently not show the appendix, so that we must first find the appendix fluoroscopically and make a roentgenogram in the position in which the appendix is visible. When the appendix remains visible for more than a day or two after the bismuth examination it is, in proportion to its poor drainage, a dangerous appendix. There are certain instances in which the bismuth shadow may persist for days, and in one or two instances it has been seen for weeks after the bismuth examination.

When visualizing the appendix the tenderness can often be localized immediately over it, and if the appendix be moved by the hand or spoon the tenderness will move with it. When the appendix is retrocecal the cecum must be pushed aside to visualize the appendix. A great majority of these retrocecal appendices show tenderness upon direct palpation. In those cases in which there is no tenderness appendicitis may usually be excluded, but if the cecum is adherent there is always a possibility that this is due to some inflammation of the appendix in the past even if the appendix is visualized and not tender. Pfahler claims that if there is localized tenderness over a fixed cecum, even if the appendix is not visualized, it means a pathologic appendix. The frequency of the visualization of the appendix by means of the bismuth meal is a much disputed point, varying according to several authorities from 35 to 90 per cent. The writers, however, do not believe every visualized appendix is necessarily pathologic. An appendix can be frequently found well-filled with bismuth, yet lying perfectly free, no signs of adhesions and the appendix emptying with the emptying of the cecum. Under certain conditions it seems there is no reason why the appendix should not fill without being pathologic. On the other hand, when we find an appendix filled with bismuth, curled up and fixed, this invariably means some pathologic process is present. When chronically inflamed an appendix is frequently adherent to the structures surrounding it. It may be fixed throughout its length or only partially so. It is a frequent occurrence to find the tip fixed with the body of the appendix lying free. If the appendix be palpated under these conditions the tenderness would indicate the presence of the chronic inflammatory process. The kinking of the appendix, which remains constant, is, according to Pfahler, a significant sign of adhesions; and when the appendix constantly points upward toward the gall-bladder region there is good ground to believe it to be in a pathologic state. The writers' experiences in this particular case agree with the findings of Pfahler. Attention has been called to the fact that in cases of chronic appendicitis, when studied fluoroscopically and radiographically, the pyloric end of the stomach is frequently observed to be lying down in the



lower right quadrant region. This is not due to adhesions but probably to the omentum wandering toward the inflammatory process. In such instances the stomach, when viewed under the fluoroscopic screen, can be moved to its normal position and yet will immediately upon release of the hand return to the lower right quadrant region. The reason for this abnormal position cannot be explained, but is probably due to some chemotactic attraction, and when present is a very definite indication of a pathologic appendix. At times, however, this position is due to adhesions from the appendix extending into the omentum, thus actually causing the stomach to be adherent in that position. We have frequently pointed out how partial obstructions of the pylorus due to inflammatory conditions are liable to lead to the production of adhesions extending to the lower right quadrant region, dragging the stomach in that direction, and thus the appendix may become secondarily affected. Adhesions associated with the appendix may, however, extend to the surrounding structures and may lead to varying degrees of cecal and ileal stasis, and even to partial colonic obstruction. While the roentgen ray renders valuable service in the diagnosis in many instances of chronic appendicitis there are a certain number of cases in which it does not demonstrate the condition or where its results may be misleading. This may be due to the fact that on account of its unusual position the appendix cannot be visualized or that its lumen is closed, due to an obliterative process, or for some reason the bismuth is prevented from entering, or there may be an absence of tenderness, especially between attacks. Both Carmen and Case have called attention to the fact that although retention of the bismuth in the appendix in plates does not necessarily always point toward a pathologic condition, yet on the other hand the appendix may be markedly diseased without being visible in the plates. In cases of subacute appendicitis, on account of the inflamed state of the appendix, the meal frequently will not enter, and there may be no adhesions. Fluoroscopically and radiographically nothing abnormal can be demonstrated in this region. The only sign that can be elicited will be tenderness over the appendix region. This tenderness, however, is also seen in a chronically distended cecum, and consequently it is not always a diagnostic sign referring to the appendix alone.

Attention must also be called to a patent source of error which should always be borne in mind. As a reflex condition a chronic appendicitis may give rise to a picture somewhat similar to that observed in duodenal ulcer; that is, there is gastric and duodenal hypermotility, with a definite filling defect and deformity of the duodenal cap; if this picture is rather marked and the appendicular adhesions are slight, one can understand how a chronic appendicitis might be mistaken for a duodenal ulcer, and in fact this error is sometimes made. In instances of this kind the plates must be most

carefully studied, repeated examinations made if necessary and in most instances a combined fluoroscopic examination, study of the plates, together with the clinical history, will point to the correct diagnosis; but even at times after a most careful investigation in every direction the correct diagnosis may still remain in doubt.

2. **Incompetent Ileocecal Valve and Ileal Stasis.** This condition is usually indicated by the fact that at the end of twenty-four hours after a bismuth meal the ileum is entirely empty, and yet at the end of thirty-six to forty-eight hours the terminal ileum is filled, indicating the presence of regurgitation from the cecum to the ileum, due to an incompetent ileocecal valve. According to Case, in about one-sixth of three thousand persons examined, most of whom were constipated and all affected with gastro-intestinal disturbances, the bismuth enema passed the ileocecal valve and filled the terminal ileum for certain distances. The ileocecal valve is normally competent and evidence of incompetency of this valve is indicated by the reflux of the bismuth meal from the colon into the ileum. Case insists that roentgenoscopic examination for this purpose must be conducted with the patient horizontal so that accurate visualized palpation may be practised under the fluorescent screen. Not infrequently, by means of massage in the antiperistaltic direction, bismuth may be forced back into the ileum from the cecum, which indicates marked incompetency.

His method of testing the competency of the valve is the following: "The patient should lie supine on the horizontal fluoroscopic table. It is not necessary to introduce the rectal point or colon tube more than one or two inches. The container should be placed not higher than two feet above the patient and the barium or bismuth enema allowed to flow by gravity, the course of the bismuth column being watched fluoroscopically. Ordinarily 1200 c.c. of the barium enema at 100° F. will suffice to fill the colon. It is important that a uniform technic be followed. I insist on seeing, by means of the fluoroscope, that the cecum is well filled. Massage of the abdomen over the shadow of the cecum is practised in the antiperistaltic direction. Still further to ensure complete filling of the cecum the patient is sometimes asked to lie on the right side for ten to fifteen minutes after the injection of bismuth, and a second examination is made when the patient returns to the table after evacuating the colon. The roentgenograms are made with the patient lying prone, plate anterior, rather than lying supine, plate anterior. In the latter position 'saddling' of the ileum over the ileocepectineal line may lead to a confusion. In marked cases of ileocolic valve insufficiency, however, there is never any difficulty in recognizing the terminal ileum." When the bismuth meal is taken it collects in about four hours in the ileum, while within eight or nine hours the ileum is normally empty of its contents. Delay in its passage may be occasioned by spasm, incompetency of the ileocecal valve, bands

of adhesions, displacements, prolapse or tumors; dilatation of the terminal portion of the ileum points to obstruction. In the study of ileal stasis care should be exercised to determine the emptying time of the stomach, inasmuch as any delay in the evacuation of the stomach may prevent the meal from reaching the ileum. When the bismuth is given by mouth and we find an actual regurgitation of the bismuth from the cecum back into the ileum, we are probably dealing with a true incompetency of the iliocecal valve. Incompetency, however, may be produced by means of the bismuth enemata if the enema is put in under too much pressure. When this is done, extremely violent antiperistaltic waves are set up which force the bismuth through the valve. The writers have repeatedly failed to demonstrate this incompetency by the bismuth meal and yet incompetency could be produced by giving the enema under forced pressure, so that one must be very careful in drawing conclusions when the examination is made by means of enemata.

**3. Dilatation of the Cecum with Retention.** When the bismuth meal is taken it ordinarily reaches the cecum in from seven to ten hours. Delay in the passage of the bismuth may be due to dilatation and retention in the cecum, which can easily be discovered by means of the roentgen ray. The cecal stasis may in some instances be associated with a chronic appendicitis, and both may, as Brown has pointed out, be due to high degrees of enteroptosis as a result of a secondary low-grade inflammatory process. The degree of cecal stasis may vary markedly in various individuals, twenty-four or even forty-eight hour retention not being unusual in some individuals. While the roentgen ray points out clearly the location of the cecum and colon, yet ptosis is a question of minor importance; similarly the position of adhesions and membrane attachments only play an important role insofar as they may lead to an interference with the function of the bowel. It is not the position of the cecum and colon with which we are most concerned but the functioning of this portion of the digestive tract, for directly in proportion to disturbances of function are symptoms of retention and partial obstruction produced.

The roentgen-ray examination of the dilated cecum has probably thrown more light upon this type of constipation than we have heretofore had. It is interesting to note that with a dilated cecum the patient may frequently not complain of constipation, on the contrary, state that the bowels move regularly every day. Yet in these cases one will find that a large part of the bismuth will remain in the cecum from forty-eight to one hundred and twenty hours. The bismuth will become almost adherent in masses to the sides of the cecum and allowing only a small channel in the center. In some of the most obstinate cases when the cecum has been explored these fecal masses are so adherent to the walls that when removed there is sometimes bleeding of the mucous membrane beneath. This must

of necessity cause a low grade of inflammation of the cecum which will frequently extend to the appendix. In such cases on operation when a chronically inflamed appendix is found, one must remember the primary cause is not in the appendix but in the cecum, and the removal of the appendix will not be of benefit to the patient.

Wilms has described a condition affecting the cecum known as mobile cecum, which is a movable atonic cecum. But little attention is now attached to this condition, for here too change in position plays but a very insignificant role; it is the adherent fixed cecum which is the seat of stasis and which is productive of symptoms.

By means of the roentgen ray and screen we are able to determine the presence of adhesions surrounding the cecum, the position of such adhesions and how far these interfere with the motility of the bowel. Important advantages are frequently obtained by means of the fluoroscopic method in the study of the cecum and its surrounding structures. By means of palpation under the fluorescent screen many important conditions may be noted. It is by this method of examination that the identification of various areas of pain on pressure, the question of motility, and separation of loops of intestines surrounding the cecum may be observed.

4. **Adhesions and Angulations.** Attention has already been called to the angulations and kinks which may occur to the lower right quadrant due to adhesions and which are usually readily recognized by means of the roentgen-ray. The adhesions may not, however, be limited to the appendix but may be associated with the cecum, at times causing marked fixation of this portion of the intestine, or may even be connected with the ascending colon or the ileum causing various degrees of obstruction, or may be due to pelvic inflammatory conditions producing a similar effect. In fact, the terminal portion of the ileum is a common seat for adhesions. On operation one frequently finds in cases of chronic appendicitis that the appendix itself is perfectly free and no adhesions are observed around the cecum, but the terminal ileum appears fixed and frequently kinked, so that the ileum beneath the kink becomes dilated and at times almost obstructed.

All of these conditions can be easily detected by the delay in the passage of the bismuth, which will be revealed in the plates, and by means of the fluoroscope.

Inasmuch as adhesions are detected by changes and delays in motility, great care must be exercised in drawing conclusions regarding these findings.

5. **Tuberculous Ulcerations.** Brown and Sampson call attention to the importance of the roentgen ray in the diagnosis of intestinal tuberculosis. According to these authors the clinical picture of intestinal tuberculosis is of little aid in the diagnosis in the early stages of this disease. On the other hand the roentgen ray may give definite information of colonic ulcerations, though the absence of the

shadows does not exclude this condition absolutely. The roentgen-ray picture presents hypermotility of the bowel, complete evacuation often occurring in from twenty to twenty-four hours, though a small amount of barium may be left in the rectum at the end of this time. In many instances Brown and Sampson found the barium in the sigmoid, the rest of the intestine being empty although a small gastric retention of bismuth was still present. In many cases the cecum and ascending colon manifested the greatest hypermotility. A most important sign is the spastic condition of the bowel involving usually the cecum and cecocolon; the bowel has also an irregular appearance presenting definite filling defects at the seat of the lesions. The presence of this intestinal hypermotility, spasm and filling defects give, according to Brown and Sampson, in a patient with pulmonary tuberculosis almost definite evidence of colonic tuberculosis.

While the above signs are associated with colonic tuberculosis, at the same time a very spastic irritable bowel will frequently be very improperly filled, due to spasm, and give almost an identical picture as that seen in tuberculosis, so that one must be extremely careful not to assume that every case of spasm and improper filling is due to tuberculosis.

**6. Ulcerations Due to Carcinoma.** In this condition there is a definite filling defect in the cecum, due to the carcinoma. This defect is large, serrated and constant in all the plates. In addition on fluoroscopic examination there is localized tenderness and fixation. Carcinoma of the cecum may exist for a long period of time before obstructive symptoms are noted. It is important in all instances to exercise great care to be positive of the roentgen-ray findings by both fluoroscopic examinations and bismuth enemata.

In a special instance which has come to our attention in which a capable roentgenologist made a diagnosis of carcinoma of the ascending colon, and in which the diagnosis was confirmed by all the methods usually practised by roentgenologists, the filling defect and partial obstruction was found due to the dragging down of the bowel by adhesions connected with an inguinal hernia.

Diagnosis of carcinoma from filling defects should never be made from a single examination. If the bowel is not completely cleared the bismuth may flow around a small mass of fecal material, which will give a filling defect. In such instances it is always well to wait several days and then have the bowels thoroughly cleansed by means of cathartics and enemata and repeat the examination. If the filling defect persists in the same position it is extremely unlikely that this is due to a bit of fecal material, but must be a true filling defect which points probably to malignancy. Small malignant masses, however, can exist in which the growth is so situated that even under the most careful examination no filling defects can be made out by means of the bismuth examination. The bismuth

enema is the method *par excellence* for examination of colonic growths. A large sized growth not producing obstruction may be frequently overlooked by means of the bismuth meal, but will almost invariably be shown by the enema method. This is particularly true when located in the descending colon and sigmoid, which are seldom properly filled when the bismuth is given by mouth.

In conclusion, we hope that we have shown the great aid afforded by the roentgen-ray examination in the diagnosis of lesions in the lower right quadrant. We must bear in mind, however, that this is but one of the many methods by which conclusions may be drawn concerning these intricate disturbances. Like all other methods of diagnosis, at times, by faulty interpretation of shadows, we may be led to a wrong conclusion. As with other lesions the lower right quadrant disturbances should be studied in conjunction with the clinical signs. If the roentgen-ray interpretation is diametrically opposed to all the clinical findings and the two methods cannot be harmonized it is probably wise to adhere to the clinical interpretation. In other words, no one method of diagnosis must be looked upon as absolute.

## ERRORS IN THE DIAGNOSIS AND TREATMENT OF DUODENAL ULCER.<sup>1</sup>

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DUODENAL ulcer without complications is to be considered in this paper.

The anamnesis will always be considered the most important single factor upon which to predicate a diagnosis of this disease. After describing the typical history, Moynihan says: "It is therefore not necessary to the attaining of a diagnosis that any examination of the patient be made; the anamnesis is everything, the physical examination is relatively nothing."

In a footnote the distinguished author disclaims any desire to eliminate an examination in the diagnostic procedure. The history accepted as typical of duodenal ulcer is well known, but as has frequently been observed, a patient may present the classic history required in Moynihan's postulate without having the disease.

A diagnosis of duodenal ulcer should never be made without a thorough general examination. One requires chemical tests of the chyme, stools, urine, a blood count, a Wassermann test and, most

<sup>1</sup> Read at the annual meeting of the American Gastro-enterological Association, May, 1920.

important of all, fluoroscopy of the chest and abdomen. Lavage eight hours after a Riegel meal is also important, indicating at times a gastric stasis not shown with barium.

No one of the above measures will prove the existence of duodenal ulcer, but all will aid in the differentiation of other diseases with similar histories.

There are no chemical changes in the chyme typical of uncomplicated duodenal ulcer. Neither has the presence of occult blood in the chyme or stool any diagnostic value.

Hemorrhage is a late complication and proves neglect on the part of the clinician.

When we cease to recognize hyperchlorhydria and gastric neurosis as entities, we will overlook fewer early cases of duodenal ulcer.

Fluoroscopy of the chest will frequently disclose an enlarged aorta. This condition, with or without symptoms of an aortitis, is often present and suggests a syphilitic duodenal ulcer or visceral lues. Either of the latter diseases is easily confused with simple chronic duodenal ulcer.

Fluoroscopy of the pylorus and duodenum is an invaluable diagnostic aid when one sees an early hyperperistalsis followed by a later hypoperistalsis and duodenal distortion.

Bourcart<sup>2</sup> has found all patients with round ulcer of duodenum have sagging viscera.

This is quite contrary to twenty years' experience in my own work. Ulcer of the duodenum has rarely been associated in my patients with visceroptosis. In fact the presence of the latter has been considered a diagnostic sign against ulcer.

A roentgen appearance of local constriction in the cap of the duodenum with local tenderness is strong evidence of duodenal ulcer.

Palpation for a tender spot should be made while the patient is in front of the screen. This is the only accurate means to associate the roentgen defect with the pain point. In fact, pressure over the tender area will often cause spasmodic contraction which may be seen in the greater curvature.

Diagnostic acumen will not be improved so long as we are content to say the patient has either duodenal ulcer, appendicitis, cholecystitis or visceral lues. In most instances, painstaking study will enable one to decide upon the correct diagnosis.

Two patients with the so-called pathognomonic history were found to have an uncomplicated cholecystitis without disease in the duodenum. The following case illustrates another error in diagnosis after a rather careful history had been secured.

On January 26, 1914, Mrs. H. L., aged thirty years, was examined. Family history is negative. She had one miscarriage at three months' gestation. Five years ago she was operated upon for ectopic

<sup>2</sup> Rev. méd. de la Suisse romande, May, 1919.

pregnancy. The appendix, one ovary and both tubes were removed. Six months ago she began to have burning, distress and eructations three or four hours after meals. The same symptoms are felt from 1 to 2 A.M. She is relieved by food or soda. The pain is never sufficiently acute to require opiates. There is occasional nausea. The appetite is good and a tendency to constipation exists. Neither vomiting, chills, fever nor jaundice has been experienced. The patient cannot eat acid foods or condiments without later distress.

Examination: Hemoglobin, 80 per cent. Erythrocytes, 4,100,000. Leukocytes, 4500. Blood-pressure: Systolic, 125 mm.; diastolic, 85 mm.

Ewald test-meal: Free hydrochloric acid, 64; total acidity, 92.

Benzidine test for occult blood markedly positive.

The stomach is empty six hours after a Riegal meal.

The stool indicates the presence of occult blood upon repeated examinations following a meat-free diet.

The urine is normal. Percussion, auscultation and fluoroscopy of chest is negative except for a slight enlargement of the aortic arch.

Fluoroscopy of the stomach reveals a persistent, rather extensive filling defect in the antrum pylori. Rectal and sigmoidoscopic examinations are negative. Diagnosis: Duodenal ulcer. An operation revealed a normal gall-bladder, pylorus and duodenum. The liver, so far as it could be observed, was covered with small yellowish-white spots.

The intra-abdominal glands were enlarged. A portion of the liver was excised, sectioned and found to show the histologic character of a gumma.

A few days after the operation a Wassermann test of the blood serum was two-plus positive, Craig system. Mercury and salvarsan effected an apparent cure, which has continued for six years.

Visceral-syphilis is frequently accountable for errors in the diagnosis of duodenal ulcer.

The above-cited case in 1914 persuaded me that a routine Wassermann test should be made upon every patient with chronic digestive disturbances. This practice has been followed for the past five years.

It is indeed surprising to note the frequency of lues as the cause of apparent duodenal ulcer.

In a review of my case records numerous instances are observed in which gastro-enterostomy failed to cure duodenal ulcer permanently. An unrecognized lues of the viscera unquestionably accounted for some failures.

Castex and Mathis<sup>3</sup> do not hesitate to affirm, on the basis of their personal observation that before the age of thirty years tardy inherited syphilis is the cause of 90 per cent. of the cases of gastric and duodenal ulcers and 10 per cent. are caused by acquired syphilis.

<sup>3</sup> Abstract, Jour. Am. Med. Assn., 1918, lxxi, 321.



My own observation does not justify this high percentage. However, until the last five years some of my diagnoses have been incorrect.

After every method of examination—laboratory tests of chyme and stool and fluoroscopy of chest and abdomen have been employed—one should make a thorough search for the stigmata of syphilis.

After making a diagnosis of duodenal ulcer, if one finds signs suggestive of syphilis the patient should be given the benefit of anti-luetic treatment. This course is indicated even in the absence of a positive Wassermann test.

Internists, as a rule, will agree that the term "cure" following gastro-enterostomy is a misnomer and should be considered "arrested cases."

Late recurrence of duodenal ulcer is more frequently observed by the internist than by the surgeon.

Errors in diet with the use of condiments and acids will often cause a recurrence of the hunger and night pain, months or even years after operation. A patient is with difficulty convinced that life-long attention to proper diet is necessary to prevent a return of ulcer after gastro-enterostomy.

Occasionally operation fails to reveal a duodenal ulcer.

A patient with a typical duodenal history was operated upon and the surgeon failed to demonstrate any evidence of ulcer. A few days later death ensued, following cerebral hemorrhage. At necropsy a linear ulcer in the posterior aspect of the duodenum, with only slight cicatrization, was seen. This patient would probably have been amenable to medical treatment.

Rigid medical treatment in a hospital should be employed before a surgical operation is undertaken. I am firmly convinced that haphazard medical treatment is responsible for many failures.

Absolute gastric rest is impossible during life, but every effort should be directed to approximate that state.

The patient should be given an effective dose of oleum ricini with the beginning of the treatment. He should then be kept in a horizontal position in bed for ten to fourteen days. During this time he must use the bed-pan and not be allowed to raise his head above the pillow. Thirst should be met with clysmata of water (not saline solution). Nutrient enemata may be added.

The duodenal tube is a foreign body near the seat of ulceration and should not be employed. It is, furthermore, usually a source of annoyance to the patient.

Alkaline drugs are well known as stimuli to gastric secretion at an interval after their ingestion, and should be omitted.

Nothing is to be given by the mouth during this ten to fourteen day period. A modified milk and oatmeal diet is then administered at frequent intervals. Quantity and variety of non-irritating foods are then added during the remainder of the four weeks' hospital

residence. At no time during the treatment is more than a three-hour interval allowed to elapse between feedings.

The patient must spend most of the four weeks in bed. Following the hospital treatment, six meals daily must be taken for at least one year. Irritating foods, such as acids, condiments and fried foods, are forbidden.

A regimen such as outlined above will arrest the symptoms and apparently cure an astonishingly large number of patients for long periods.

After the physician has convinced himself by antiluetic treatment or by rest cure in bed, or by both, that the patient is unimproved; then and then only should a surgical operation be undertaken.

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### CORRECTIONS VERSUS COMPENSATION OF PHYSICAL DEFECTS.

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THE inauguration of a program of required physical training for Freshmen in Harvard College necessitated a survey of the general methods already in use. A scrutiny of the multitude of methods employed in many places readily showed there is no generally accepted agreement as to the fundamental principles involved in physical training. There was, of course, a common agreement that physical training is generally beneficial. Most people accept the dictum that the human body is definitely benefited by regular physical exercise. It is also generally agreed that the benefits of physical exercise can be traced to the mind as well as to the body. There is, however, no agreement as to the proper methods to be pursued in attaining this end. As a matter of fact the discussion and also the practice of the procedure to attain the general end of improved bodily condition is very largely concerned with a discussion of methods and fails to take into account the underlying principles. One finds that calisthenics, special gymnasium work, military drill and every form of sport are each heartily recommended as the best method of achieving beneficial physical effects from physical training.

It has seemed to us that methods were entirely secondary to the underlying principles. It has seemed to us that muscular exercise represented by so many foot pounds of work could be performed in a wide variety of ways. It also has seemed to us that the delivery

of muscular exercise was in a sense a prescription which should be based upon an intelligent examination of individuals. In other words, there is probably no blanket prescription, even though one may have to utilize, when dealing with large numbers of individuals, what may be called group prescriptions. The ideal method would be, of course, to base a prescription upon each individual case, and like any medicinal prescription, such prescription takes into account special factors as convenience, palatability, etc. Physicians do not write prescriptions for pills of such a size that they are too large to swallow, nor do they write prescriptions in fluid form for drugs which have a very bad taste which can be concealed under an appropriate coating. A prescription for physical training therefore may justifiably be governed by convenience and palatability as well as by other considerations.

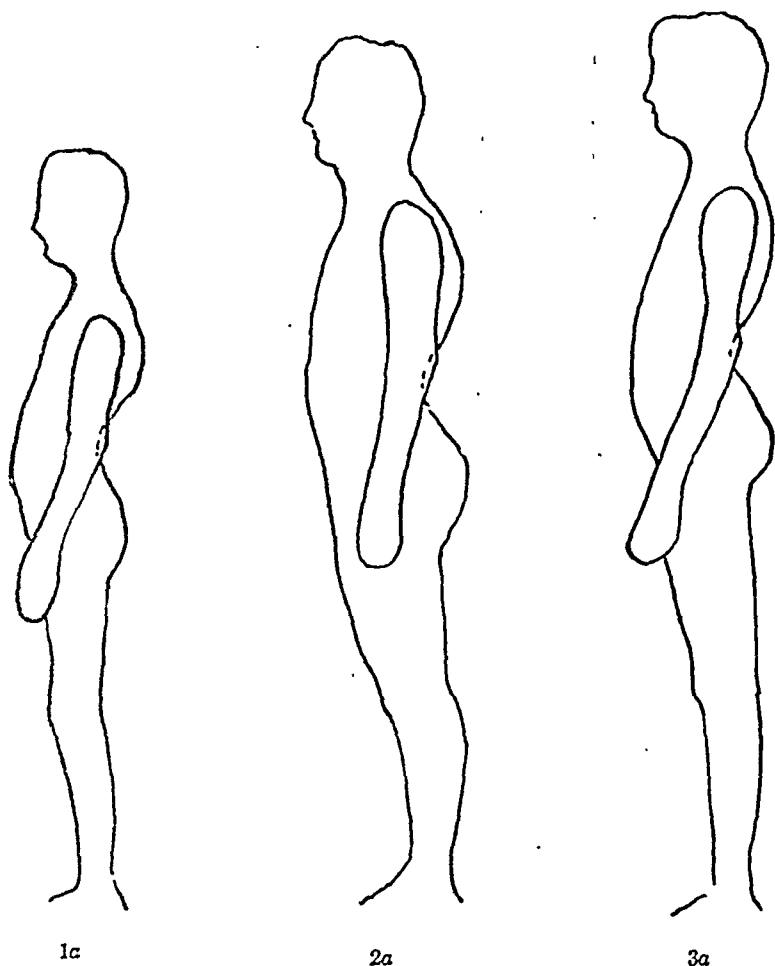
As a preliminary to our prescriptions for physical training we have made a complete medical physical examination. This examination naturally revealed a certain amount of organic defects, some of which were capable of being corrected by standard medical procedures. A certain number of these organic defects, however, might be benefited by physical exercise, even though they were permanent and not capable of correction by ordinary medical therapeutics or by physical training therapeutics. Such defects were at once classified as permanent defects not capable of correction but capable of adequate compensation. In connection with the medical physical examination the individuals were also examined from the point of view of bodily mechanics which took into consideration two factors, namely, the use of the body in the standing position and the use of the feet. The discussion of the classification of bodily mechanics and the general outline of the subsequent procedure has been made in another communication.<sup>1</sup> In summary it was found that 20 per cent. of Harvard Freshmen had satisfactory use of the body, while in 80 per cent. the use of the body was classified as being unsatisfactory. It is evident, therefore, that in the case of 20 per cent. of the individuals the immediate problem was merely that of delivery of physical exercise in order to maintain the satisfactory use of the body. To our minds the method of physical training is of no importance as an immediate problem in those individuals. The method of physical training is of some importance as a life problem looked at from the point of view that it is desirable to encourage individuals to develop satisfactory habits of physical exercise. From that point of view there is a definite choice of methods. It is obviously desirable to encourage some habit of physical exercise which can be maintained at least throughout the early part of adult life. But, as we have said, the immediate

<sup>1</sup> Brown, L. T.: *Am. Jour. Orthop. Surgery*, 1917, xv, 774. Lee, R. L., Brown, L. T., and Geer, W. H.: *In press*. *American Physical Education Review*.

problem in those individuals does not particularly concern methods. In the 80 per cent. of individuals who use their bodies in a more or less unsatisfactory fashion there are definitely two problems, (1) the problem of correction, and (2) the problem of furnishing physical exercise.

It is noteworthy there is no positive relationship between the muscular strength of the individual and the participation in physical exercise on the one hand and good bodily mechanics on the other. In other words, while those who use their bodies properly tended to have participated in some form of physical exercise and to have well-exercised muscles, nevertheless very muscular and very athletic individuals were also found who used their bodies in a very poor fashion. The general, though not the universal, tendency has been to accept powerful musculature and the habit of physical exercise as approximately equivalent to a satisfactory use of the body. Our investigations have failed signally to establish this contention. At the very first we were impressed with the fact that only a small portion of those who use their bodies in an unsatisfactory fashion had symptoms from this unsatisfactory use. At that time the employment of the term "compensated defects" began. It was evident that there was a definite comparison between a heart lesion and a bodily lesion. There are many individuals with heart trouble who are in the stage of a compensated heart defect. Nearly all individuals with heart lesions have an early period of compensation and a goodly proportion continue their compensation throughout life. This compensation may be of a greater or less degree. The comparison holds true of bodily defects. It is possible by good musculature to compensate for bodily defects and to maintain this compensation throughout life. This compensation is likewise of varying degree. A concrete example may be given: C. W. had infantile paralysis in early life, with a resulting marked deformity of his back. He enlisted early in the war, was accepted and served throughout the war without difficulty. He had big muscles and gave the external appearance when dressed of a large, powerful young man. After the war he came to college and took up football, which he had played in preparatory school without difficulty. Hard scrimmaging, however, brought on very definite symptoms in his back. Despite his powerful muscles it soon became apparent that he had adequate compensation for the routine work in life, even for army life, but the compensation of his back defect was not adequate to enable him to play college football. Inasmuch as his defect was structural it was not capable of correction but was merely capable of compensation. It is therefore in this instance necessary to accept compensation as the sole program. The case of F. R. may be utilized as a further illustration. F. R. is a powerful youth with big muscles who has participated in all forms of games and exercise. On examination he is classified as "D," or as having very bad

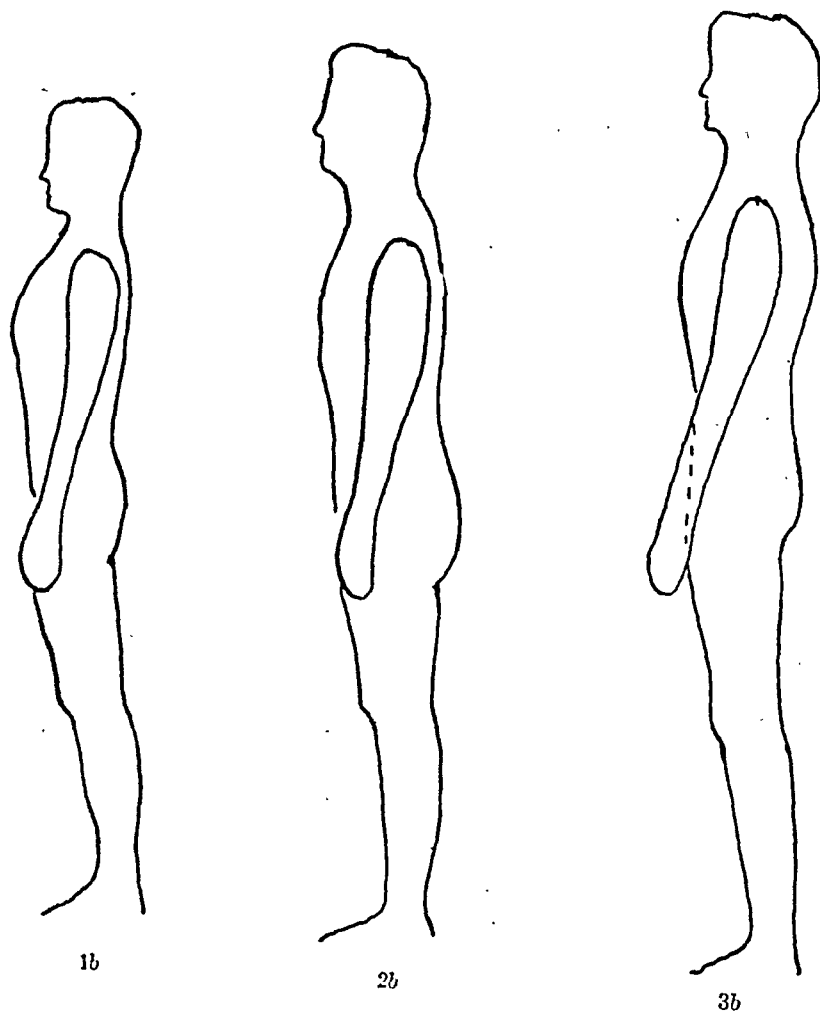
mechanical use of the body, because he has very unsatisfactory position of his body in standing, and he furthermore uses his feet in an unsatisfactory fashion. The young man has built up an excellent degree of compensation for his functional defects. When he first presented himself he was inclined to be indignant with his classification. It was of course to be expected that he had had no trouble with his back or with his feet. He was put in a group for special



instruction in regard to bodily mechanics. In the meantime he continued his usual vigorous athletic activities. He appeared one day complaining of his feet. To be sure, he had poor boots which in our experience is often the determining factor between compensation and failure of compensation in individuals who use their feet poorly. But the fact remains that despite vigorous athletic exercise and despite his powerful muscles his bodily mechanics failed because he did not use his feet correctly. He has now had his intensive

instruction in bodily mechanics, and it is hoped that he will have his bodily mechanics corrected. Upon the foundation of corrected bodily mechanics he will have physical training which will not compensate for his defects, but will establish more firmly his corrected bodily mechanics.

It has been our experience that back defects are usually fairly well compensated throughout young adult life. We believe this to



be almost unfortunate because it gives a false feeling of security, and it permits a bad habit to be very firmly fixed. Consequently, when in later life with a diminishing muscular power compensation fails, correction is often difficult and the fixation of the corrected bodily mechanics by habit and by physical exercise may be next to impossible to achieve.

In the case of the bodily mechanics of the feet the question of compensation and correction is somewhat different. It is decidedly

more simple to compensate bad mechanics of the feet by the use of tight shoes or by plates than it is to correct their bad mechanics by sheer muscular power. Consequently when compensation for the mechanical defects of the feet has been lost the individual is often led to try out a large variety of shoes and plates, with the hope of restoring it. Compensation thus restored is always a potential of future trouble unless it is followed by the fixation of correct mechanics by education, habit and physical exercise.

We believe that it is because the results of bad use of the feet are relatively so promptly evident that, on the whole, sounder opinions prevail in regard to correction versus compensation in the feet than in the back; but to our minds the same fundamental principles underlie every form of bodily mechanics. In our program we emphasize correction of all defects when present. Compensation is reserved for irremediable defects such as structural changes of the back. Following correction we insist upon the fixation of correction, by physical exercise in the corrected position, and following this stage we encourage general, all-around physical exercise in order to fix more firmly the corrected habit. In other words the stages are, 1, correction; 2, fixation of correction; 3, the habit of exercise in the corrected position; 4, firm fixation of corrected habits. Our experience has confirmed this theoretical consideration because we have not found that faulty habits of bodily mechanics tend to be corrected to any extent by simple exercise. Therefore in the required course of physical training we demonstrate to each individual separately the proper method of standing even if he stands correctly. The class, as a whole, is given lectures demonstrating the principles of bodily mechanics. So far our program for further work has only embraced those who presented very bad bodily mechanics. These individuals are divided into small groups and receive intensive instruction. The result of this instruction has been very satisfactory, as will be seen from the accompanying illustrative charts. Fig. 1a, 2a, 3a, positions assumed by three students at the time of their first examination. Fig. 1b, 2b, 3b, positions assumed by same students after receiving instruction in bodily mechanics when told to stand as well as they could.

These tracings were taken at random from a large series and bring out the fact that although the student started with no knowledge of correct bodily mechanics, at the end of his course of instruction he not only understood the theory of it but could give a practical demonstration.

It is not always possible to achieve satisfactory success with each individual, but it is exceptional that we have not been able to change those classified as "D," or very bad mechanical use of the body into a classification of "B," which means good mechanical use of the body. It will be noted that we have concerned ourselves mainly

with the 25 per cent. who presented the very bad mechanical use of the body. Since the program was tentative and experimental it was decided to await the result of a year's experience in order to see what a single personal demonstration and general lectures would do for the big group of young men classified as "C" who had moderately unsatisfactory mechanical use of the body. While it is true that a considerable number of these were energetic enough to correct themselves, nevertheless the general error of preferring compensation to correction was the more common. We now believe that it is necessary to broaden the intensive instruction so as to include the "C" group as well as the "D" group. This will be put into operation in another year.

We would like to emphasize the importance of a proper nomenclature in any system of physical training. A discussion which involves nomenclature has certain obvious advantages and disadvantages. In general the disadvantages far outweigh the advantages. After all the purpose of nomenclature is to clarify one's conception. Nomenclature *per se* has no particular value. It is only of use when utilized as a means to an end. Too often nomenclature becomes the end and not the means, and a discussion of nomenclature becomes distasteful because it is synonymous with quibbling. Also, it not infrequently suggests that a knowledge of nomenclature is a knowledge of the subject-matter concerned. In the present discussion it is believed that the nomenclature as outlined in the title, corrections or compensation of physical defects, is of some real assistance in the understanding of the subject-matter concerned.

In order to be really successful a physical training program must be based upon careful examination, and this careful examination must be directed toward bodily mechanics with as much care as it is directed toward the heart. Actual structural defects which cannot be corrected and which require compensation are just about as frequent as organic disease of the heart, which likewise cannot be corrected and must be compensated. Judging by our statistics we may assume that the majority of individuals have habits of poor mechanical use of the body, and if left to themselves these individuals may increase compensation but will not correct their defects. It is important that the actual program of physical training be based upon an examination of bodily mechanics. It is possible to give prescriptions for groups of individuals as a result of this examination. All individuals who have poor mechanical use of the body will require as a part of their prescription a preliminary correction. One may expect to see fairly quickly the demonstration of the advantage of correction over compensation in the mechanical use of the feet that is fairly well explained. The same general principle holds true of the mechanical use of the back, but because compensation usually persists for a number of years the untoward effects in the



form of definite symptoms from the bad mechanical use of the back are usually slow in coming. It is possible, however, to correct bad mechanical use of the back, and it is possible to fix rather firmly good habits even in the most unpromising individuals.

We are not prepared at this time to support the theory that many ailments of the nervous system or of the gastro-intestinal system are related to bad mechanical use of the body. We can, however, state that there is a frequent association of such symptoms with the mechanical use of the body. Our investigations have shown that albuminuria of young men which is not a true nephritis is associated almost exclusively with very bad mechanical use of the body. We believe that a sufficient case can be made out for correction as against compensation on the basis of actual ailments of the back and feet, generally conceded to be due to faulty use of the body even without the addition of possible symptoms connected with other organs.

We believe that physical training can only accomplish what it is expected to accomplish when it is based upon satisfactory fundamental principles and when bodily mechanics is regarded in a similar fashion as the disturbances of any other system of the body are regarded.

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## A CLINICAL STUDY OF WASSERMANN-FAST SYPHILIS, WITH SPECIAL REFERENCE TO PROGNOSIS AND TREATMENT.<sup>1</sup>

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THE so-called Wassermann-fast syphilitic infection will probably attract increasing attention as the time during which modern methods of treatment have been employed lengthens and methods of intensifying the sensitiveness of the test demonstrate a smaller and smaller proportion of permanent negatives. A recent survey of the literature following a study of a group of apparently Wassermann-fast cases under treatment in the Section of Dermatology seems to suggest that while Wassermann-fastness is a type of syphilologic tradition, relatively little attention has been paid to critical clinical study of these cases, with a view to ascertaining the types of syphilis that may be expected to give rise to resistant positive reactions in the blood and whether the superficially asymptomatic character of

<sup>1</sup> Presented before the Central Interurban Clinical Club, Rochester, May, 1920.

certain of such cases is borne out by complete investigation. Without any predispositions on the matter we undertook to analyze the clinical picture presented by 101 apparently resistant infections, observed among 458 patients who had received more than twelve intravenous injections of arsphenamin, with appropriate interim mercurialization. While we do not suggest that the amount of treatment these patients received is to be regarded as conclusive evidence that they are Wassermann-fast, our experience has tended to show that patients who do not undergo a reversal of the blood Wassermann with this amount of treatment are likely to present resistant characteristics and will probably not be made negative without the employment of an amount of treatment which raises the question of the possibility of therapeutic injury instead of benefit. Kaplan, particularly, has been outspoken in his injunctions against attempting to reverse Wassermann-fast cases. Craig, on the other hand, has very properly emphasized the searching clinical examination, which must be made before a persistently positive blood Wassermann can be regarded as a solitary and insignificant symptom. It is to be feared that the decline in confidence which seems to have affected the persistent negative Wassermann as evidence of cure may have undesirable by-effects in a tendency to underestimate the persistent positive Wassermann as evidence of the clinical activity of the disease.

The 101 cases employed in this study were obtained from our records without predisposition with regard to the findings and have served as a valuable index of the lacks in completeness in our syphilologic examination. Particularly do we believe that closer attention to the condition of the cardiovascular system in patients with signs of resistant syphilitic infection will show that this group of structures may be the seat of pathologic change when the grosser visible manifestations such as cutaneous, osseous, and neurologic involvements have been brought under therapeutic control.

It is of interest to note that of the 101 cases in which serum Wassermann reactions resisted the amount of treatment described, only four (3.9 per cent.) were florid secondary cases at the time treatment was begun. The remaining 96.1 per cent. included, therefore, Wassermann positive latent cases and various forms of osseous, visceral, cutaneous, and neurologic syphilis and lues hereditaria. Data on the duration of the infection up to the time treatment on this service was begun were obtainable in only 35 per cent. of the cases, the period ranging from two months to twenty-four years, with an average duration of thirteen years. The duration of the presenting symptom averaged two and a half years (in 101 cases). The group, as a whole, therefore, is to be regarded as made up primarily of late syphilis.

**Methods of Examination.** The methods of examination employed in this group of cases included various combinations of twenty-one

different groups of procedures (Table I). Since the work was undertaken without premeditation very few of the patients had routine or complete examinations as judged from such a schedule. On the other hand the majority of the examinations were more complete than in the average studies of syphilitic infections. The tabulations include the number of cases in which data were available in each type of special examination employed. It should be stated that the Wassermann test employed was performed under the direction of Sanford and consisted of a single Noguchi antigen test, using a rabbit-human hemolytic system with active serum and incubator fixation. Experience has shown this technic to be conservative so that fixed positives obtained with it would, with little doubt, prove persistently positive with any technic employing more highly fortified and multiple antigens or cold fixation.

TABLE I.—THE MULTIPLE PROCEDURE DIAGNOSTIC ATTACK ON SYPHILIS.

1. Intensive study of anamnesis.
2. The social estimation of the case.
3. The study of the family both in history and examination.
4. The serum Wassermann reaction (single antigen).
5. Modifications and intensifications of the serum Wassermann test, such as the provocative, cold fixation, multiple antigens, and Wassermann series.
6. The examination of the cerebrospinal fluid (two Wassermann tests, Nonne, cell count on the fresh fluid, colloidal gold test).
7. The dark-field examination and stains of fresh secretions.
8. The luetin test.
9. The Levaditi and other tissue stains.
10. The neurologic examination.
11. The eye examination.
12. The ear examination.
13. The nose and throat examination.
14. The dermatologic examination of the skin and mucous membranes.
15. Visceropathic studies of the liver and spleen and of the stomach, involving the study of anemias, blood dyscrasias, test-meals, esophagoscopy, roentgen examination, and so forth.
16. The special cardiovascular examination, including the physical findings, blood-pressure, electrocardiographic examination.
17. The reentrenologic examination.
18. Exploratory operative procedures (seldom used until after the therapeutic test).
19. Genito-urinary examination.
20. The therapeutic test.
21. Necropsy.

Table II indicates the number of patients in the Wassermann-fast group who were specially examined for the types of systemic involvement mentioned with the percentage showing syphilitic involvement before treatment was begun.

It will be apparent at once from Table II that cardiovascular syphilis among the patients specially examined for this form of involvement is the principal type of syphilis associated with a resistant positive Wassermann. This finding is in accord with the

observations of Brown on the importance of a search for signs of aortitis in patients who are apparently Wassermann-fast. Of the group of thirty-five patients who had cardiovascular examinations 66 per cent. showed signs of early aortitis and 60 per cent. myocardial changes. There were no patients with hypertension (systolic blood-pressure over 140). It has seemed to us that the more we make systematic cardiovascular examinations of Wassermann-fast patients the more pathology we find. It is, of course, conceivable that a close inquiry into certain symptoms is directing our attention toward this group and allowing to pass unnoticed an equal grade of involvement in some more silent organ, such as the liver or spleen. Syphilis of the central nervous system and syphilis of the osseous system take second place in our experience, in spite of the belief voiced by Kaplan, for example, that a neurologic and cerebrospinal fluid examination in serum Wassermann-fast cases is likely to disclose evidence of general paresis. In 67 of the group of 70 patients who presented evidence of neurosyphilis, examination of both the cerebrospinal fluid and the nervous system was carried out and one or the other examination was done in the remaining 3. Of the twenty-one patients with neurosyphilis underlying their resistance to treatment 40 per cent. have proved to have paresis, 50 per cent. tabes, and 10 per cent. early cerebrospinal syphilis. It is, of course, conceivable that an unascertained proportion of the patients with resistant neurosyphilis of other clinical types than paresis will ultimately develop paresis. Attention will be called to the fact that cardiovascular and neurosyphilis are by no means mutually exclusive, since half the patients with neurosyphilis also had cardiovascular lesions.

TABLE II.—100 WASSERMANN-FAST(?) CASES; TABLE OF STRUCTURES PRESENTING EVIDENCE OF SYPHILITIC INVOLVEMENT BEFORE TREATMENT WAS BEGUN.

System involved.	Number of cases examined.	Percentage showing syphilitic involvement.
Cardiovascular . . . . .	35 <sup>1</sup>	44
Central nervous system . . . . .	70 <sup>2</sup>	30
Osseous . . . . .	100 <sup>3</sup>	30
Visceral (hepatic, splenic and gastric) . . . . .	100	21
Cutaneous and mucous membrane . . . . .	100	17
Lues hereditaria . . . . .	100	10
Lues latens (positive Wassermann only) . . . . .	100	10

<sup>1</sup> Only the cases receiving special examination by Willius are considered.

<sup>2</sup> Only patients receiving special examination by Sheldon or spinal puncture, or both are considered.

<sup>3</sup> Does not include any routine roentgenologic examination.

The patients presenting osseous involvement failed to show any distinctive type of bone changes standing out preëminent in the

group. Visceral involvement was represented by twenty-one patients, 52 per cent. of whom had gastric syphilis, 47 per cent. hepatic syphilis, and 14 per cent. splenic involvement. The large margin of error introduced into the proportions of hepatic and splenic syphilis by the impossibility of detecting by physical examination lesser degrees of involvement than those necessary to produce palpable tumor or recognizable symptoms must be borne in mind.

Cutaneous symptoms appeared in only 17 per cent. of the cases in our series, and in none of these was the cutaneous condition the sole manifestation of syphilis apart from the positive Wassermann. Nodular and infiltrative lesions served, on several occasions, as valuable clues to the infection, which in the absence of a gross indication for a Wassermann might have passed unrecognized. A particularly large percentage (50) in this group proved, on special cardiovascular examination, to present positive signs, a point which emphasizes the danger of skin-deep interpretation of syphilis and the imperative need to look back of the seemingly easily identified manifestations when a symptom such as Wassermann fastness appears. Only a small proportion (6 per cent.) of the resistant cases with cutaneous involvement presented evidence of neurosyphilis.

Heredosyphilis and syphilis whose existence is evidenced solely by a positive serum Wassermann reaction occupy only a small place among our resistant infections (10 per cent. each).

It is apparent, therefore, that Wassermann-resistant syphilis, far from being trivial or therapeutically minimizable syphilis, is synonymous with grave syphilis, involvement of the cardiovascular system, the nervous and the osseous structures, and the large viscera, constituting 70 per cent. of the total involvement.

Wassermann-resistant late syphilis, in addition to being grave syphilis, is polysymptomatic or exhibits a tendency to multiple structural involvement. This point is best brought out in Table III, in which each type of involvement is cross-indexed, so to speak, to the percentage of other forms of structural involvement associated with the presenting type. For example a patient whose presenting symptom was gummatous osteitis might be found on intensive study to have likewise a neurosyphilis and cardiovascular evidences of his infection. Complications of this sort whose clinical recognition should be the result of multiple diagnostic attack (Table I) have in the past been more conspicuous in the postmortem room than at the bedside, to the discomfiture of the clinician. Failure to recognize such complications during life should become increasingly rare as our clinical diagnostic armamentarium is improved and utilized.

We believe that it is worth while at this point to comment on the gradual approximation of clinical findings to necropsy findings which

can be brought about by the use of group diagnosis in syphilis. To our minds there can be no more convincing evidence that syphilologic diagnosis will never resolve itself into the performance of any single technical test. We believe the logical method for identifying clinical syphilis in obscure cases is identical with that employed in the determination of the types of involvement in our Wassermann-fast cases, and consists essentially of a series of examinations by specialists, each expert in some particular phase of the disease. The results of such composite examination, and particularly the apparent demonstration that Wassermann-fast syphilis is a grave rather than a harmless affair, should compel the greatest conservatism in *ex cathedra* statements regarding the significance of seemingly monosymptomatic positive Wassermans. Those who are inclined to interpret Wassermann positiveness as a favorable evidence of a high resistance to the infection, and hence of a probable freedom from complications, must, it seems to us, at least subject their material to the most searching and critical examination for every type of involvement before their conclusions can deserve general acceptance. That rash statements with regard to the insignificance of a fixed positive Wassermann may do harm and are to be discouraged until further evidence of its real meaning is available seems to us equally apparent.

TABLE III.—MULTIPLE STRUCTURAL INVOLVEMENT PRESENT IN EACH OF SIX TYPES OF SYPHILIS.

Of 15 patients with cardiovascular syphilis.
20 per cent. also had neurosyphilis.
20 per cent. also had osseous syphilis.
20 per cent. also had cutaneous and mucous membrane syphilis.
6 per cent. also had heredosyphilis.
6 per cent. also had splenic, hepatic or gastric syphilis.
Of 21 patients with neurosyphilis.
50 per cent. also had cardiovascular syphilis (of 6 specially examined).
18 per cent. also had osseous syphilis.
14 per cent. also had splenic, hepatic or gastric syphilis.
4.6 per cent. also had cutaneous syphilis.
Of 30 patients with osseous syphilis.
43 per cent. also had cardiovascular syphilis (of 6 specially examined).
17 per cent. also had cutaneous syphilis.
13 per cent. also had neurosyphilis.
10 per cent. also had visceral syphilis.
Of 21 patients with visceral syphilis (splenic, hepatic or gastric).
14 per cent. also had cardiovascular syphilis (of 7 specially examined).
25 per cent. also had neurosyphilis.
14 per cent. also had osseous syphilis.
Of 17 patients with cutaneous and mucous membrane syphilis.
50 per cent. also had cardiovascular syphilis (of 6 specially examined).
6 per cent. also had neurosyphilis.
50 per cent. also had osseous syphilis.
Of 10 patients with heredosyphilis.
33 per cent. also had cardiovascular syphilis (only 3 specially examined).
20 per cent. also had neurosyphilis.
20 per cent. also had osseous syphilis.
40 per cent. also had interstitial keratitis.
50 per cent. also had eighth nerve deafness.

Three points stand out conspicuously from the foregoing study: (1) The more carefully the search for cardiovascular syphilis is carried out in Wassermann-fast cases which exhibit other signs of active disease on first examination the more often cardiovascular syphilis is recognized. This finding is in accord with necropsy experience with syphilis in general, as presented by Warthin, Symmers and others. The former in particular found the heart and aorta involved to some degree in every case and rates myocarditis as the most common cause of death from syphilis. (2) Wassermann-resistant patients who have some definite clinical manifestation of syphilis as a presenting symptom on superficial examination are likely to exhibit multiple types of involvement on complete examination. The type of infection presenting a resistant positive Wassermann is therefore probably not produced by a special strain of organism, and Wassermann fastness should therefore probably be interpreted less as a single symptom than as a guide to an underlying multiplicity of symptoms. The conspicuous exception is the long-recognized inverse relationship between cutaneous and neurosyphilis which seems to be the only example of a mutually exclusive combination in the series. (3) The last point suggested by this study is that there is a curious, almost paradoxical contrast between syphilis whose only symptom after careful examination is a positive Wassermann and syphilis with both active lesions and a positive Wassermann whose resistant character becomes apparent only after treatment. Our group of such pure latent cases is too small and our period of observation too short to justify a prediction as to whether these patients will ever develop active manifestations. We do not therefore offer here any generalizations on the possible protective significance of the monosymptomatic serum Wassermann. That only 10 per cent. of such monosymptomatic Wassermans appeared in our series suggests at least that the group in which Wassermann-fastness can be dismissed as meaningless is very small.

Certain incidental observations from our series are based on groups of cases too small as yet to deserve detailed analysis. One such interesting incidental finding was the presence of septic foci in teeth, tonsils, and elsewhere in 74 per cent. of the cases. We are not prepared to suggest the relation of this detail to the resistant Wassermann or to the polysymptomatic character of the infections in this group. In 29 per cent. of the cases the foci were removed without effect on the Wassermann. Only 12 per cent. of the patients were users of alcohol. In view of the well-known inhibitory effect of acute alcoholism on the positive serum-Wassermann reaction such a finding may ultimately prove of interest. There was no evidence that pregnancy and childbearing had any relation to the resistant Wassermann reaction.

**Treatment of the Resistant Wassermann Patients.** It will be recalled that for the purposes of this paper we defined our Wassermann resistant group as consisting of those cases which were not permanently reversed to negative in the blood by a minimum of twelve injections of arsphenamin and interim mercurialization by inunction. This amount of treatment left Wassermann positive only four of the early cases seen on the service. It appears, therefore, that the resistant Wassermann in our experience is a manifestation of late syphilis (average duration of disease thirteen years in 35 cases and of symptoms two and a half years in 90 cases). An analytical *resumé* of our treatment technic in these cases is as follows:

Minimum number of arsphenamin injections . . .	12
Maximum number of arsphenamin injections . . .	29
Average number of injections for each patient . . .	14
Average number of injections for each course . . .	6
Average number of courses for each patient . . .	2½
Average period over which the above treatment was given . . .	11 months
Average interval between injections . . .	1 week
Average total duration of arsphenamin treatment . . .	2½ months
Average number of inunctions given (90 patients) . . .	90, 4 gm. 33 per cent.
Average number of inunctions given for each course . . .	40
Average number of succinimid injections given (21 patients) . . .	21, ½ gr. daily
Average total duration of inunction treatment . . .	4½ months

Summarizing, it appears that the average Wassermann resistant patient in our series remained Wassermann positive after fourteen arsphenamin injections and ninety 4 gm. 33 per cent. inunctions administered intermittently in eleven months and equivalent to about six months' continuous treatment. It should be mentioned that we often employ arsphenamin and mercury simultaneously, thus shortening the continuous period as compared with the intermittent period.

This amount of treatment, then, has secured the reversal of about 96 per cent. of our early cases and 78 per cent. of our late cases. It is interesting, for example, that Detweiler reports 57 per cent. of a large series reversed by eight injections of diarsenol. The fallacy of comparisons between such series is easily appreciated by recalling that the serum-Wassermann reaction has no standard meaning for all observers. An insensitive test which is a valuable guide to Wassermann fastness is a poor guide to therapeutic effect, since in the former it picks out as fixed positives cases whose Wassermann reactions would certainly be positive with hypersensitive antigens or cold fixation, while in the latter it results in premature negatives which a sensitive technic would still recognize as positives. An observer using a hypersensitive Wassermann therefore secures fewer reversals than one using a conservative technic. We find ourselves in full accord with Wile and Hasley in refusing to accept



even a persistent negative Wassermann reaction as evidence of cure, since its meaning is largely a matter of technic. The present study, however, compels us to reserve our opinion on their espousal of the obverse view that "in the presence of an intensive therapy a positive test does not mean living spirochetes and a potential syphilis."

So far as symptomatic therapeutic effects are concerned the clinical results in our series of 101 Wassermann-resistant cases were much more satisfactory than the serologic. In 84 per cent., in spite of the persistent positive Wassermann, the infection was symptomatically arrested *pro tempore* and the visible lesions disappeared. In 16 per cent. the disease continued to progress or clinical evidence of active syphilis persisted. Of the 16 patients not responding to the above therapy, 6 had paresis, 3 had gastric crises in tabes dorsalis, 2 had cerebrospinal syphilis, 2 had interstitial hepatitis, 1 cyclic vomiting, 1 myocardial degeneration, and 1 a persistent anemia. We wish to enjoin conservatism in the attempt to make ultimate interpretations of the above results. Regardless of the degree of symptomatic improvement achieved no one of our series of patients will be voluntarily dismissed by us from observation throughout life.

The question of the amount of treatment which it is proper to administer to a Wassermann-resistant patient is no more susceptible of exact definition and reply than are the many other questions centering around the problem of standard procedures in syphilotherapy. With the immunologic meaning of the complement-deviation test still obscure, the first essential to a decision is lacking. The second essential, too generally overlooked, is almost as far from adequate understanding. Until we have a more exact comprehension of the harm which excessive treatment may inflict on the body, and notably on the excretory mechanism and on tissues on which the treatment employed has a selective toxic effect, we cannot, at least in late and Wassermann-fast cases, make that exact estimation of balance between the potential evils of the disease and the evils of therapy which the occasion demands. We have therefore adopted as guides to treatment tentative principles as follows:

1. Search every accessible organ and tissue in the Wassermann-fast case by every clinically available method for evidence of syphilitic changes.

2. Weigh the degree of activity of the process and the extent of damage and probable recuperative power of the most vital structure involved by the infection.

3. Identify the weakest element in the patient's make up and estimate the tolerance for arsenic and mercury of the structures which must bear the brunt of treatment by-effects, such as the liver, kidney, and skin.

4. Do all that can be done to increase tolerance of treatment by protective measures, by extirpation of focal infection and by selection of the therapeutic agents.

5. Direct the treatment of Wassermann-resistant patients less toward overcoming the resistance offered by the Wassermann reaction and more toward a satisfactory symptomatic response of the vital structures involved by the disease within the limitations imposed by the weakest element in the tolerance. Get all the symptomatic effect possible short of recognizable damage. If tolerance permits give at least as much treatment as to a fully developed secondary case.

6. Recall the fallibility of human judgment, which in syphilotherapy at least has had neither the time nor the means to achieve conclusive results, and always regard the Wassermann-fast patient as potentially syphilitic, and for that reason not to be dismissed from careful search for evidence of activity at intervals throughout life.

Summary. 1. Of 458 syphilitic patients who had received from twelve to twenty-nine arsphenamin injections combined with mercurial inunctions, the average being fourteen injections and ninety inunctions in eleven months, 6.6 per cent. of primary and secondary cases and 101, 22 per cent., of latent, late and hereditary cases (average duration thirteen years) remained persistently Wassermann positive.

2. Cardiovascular changes are apparently those most likely to underlie a resistant positive Wassermann test in late syphilis (44 per cent.), with neurosyphilis 30 per cent., osseous lesions 30 per cent., hepatic, splenic, and gastric syphilis 21 per cent., and other types from 10 to 17 per cent.

3. More than one type of involvement was the rule in the individual cases of this group. There were only 10 patients presenting no other evidence of syphilis than their positive Wassermans.

4. Patients with syphilis should therefore be studied from other angles than that of the presenting type of involvement, in the effort properly to appraise their condition and susceptibility to treatment.

5. Sixty-five per cent. of the patients with cardiovascular syphilis had aortitis and 60 per cent. myocardial changes.

6. Of the neurosyphilitics, 40 per cent. had paresis and 50 per cent. clinical tabes dorsalis.

7. Fifty per cent. of patients with neurosyphilis had cardiovascular syphilis also.

8. Gastric and hepatic syphilis were recognized in 52 and 47 per cent. of the visceral cases as against only 14 per cent. presenting recognizable splenic involvement. Patients with cutaneous syphilis showed the familiar immunity from neurosyphilis and the reverse.

9. While pyogenic foci were present in 74 per cent. of the patients with resistant-Wassermann reactions no frank etiologic connection

was apparent. The same was true of alcohol, which was used by only 12 per cent. of these patients.

10. There was no evidence that Wassermann-fastness is the result of infection with any special strain of organism. In fact, the "polystructural" involvement in such cases suggests the contrary.

11. Eighty-four per cent. of the patients in our Wassermann-resistant group have undergone symptomatic arrest today under the treatment received. Paresis and tabes dorsalis with gastric crises formed more than half the failures.

12. The amount of treatment to which a Wassermann-resistant patient should be subjected cannot be exactly defined. The principles employed in making a decision, which are in effect the principles underlying the therapy of all late syphilis, are outlined on page 666. In particular, reversal of the Wassermann, while desirable, should not be the primary aim of the therapy. Symptomatic response, with arrest of the process, and the giving of as much treatment as to an early case, provided tolerance permits, are the important considerations.

13. A persistently positive serum Wassermann reaction seems to be an accompaniment of grave rather than of trivial syphilis. At least such is the case in enough instances to suggest the need for the most painstaking and repeated investigation of the clinical aspects of the Wassermann-fast case. Premature statements based on insufficient evidence as to the insignificance of a fixed positive Wassermann reaction are, we believe, to be deprecated.

14. Wassermann-fast patients should not, in our opinion, be discharged from periodic careful reëxamination, with special reference to the cardiovascular and nervous systems throughout life. The frequency of such examinations should be dictated by the gravity and extent of the original process and the degree of apparent resistance to treatment.

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**INFLUENZA PNEUMONIA: CERTAIN RADIOLOGICAL FEATURES  
OF THE DISEASE IN THE EPIDEMIC OF 1920.**

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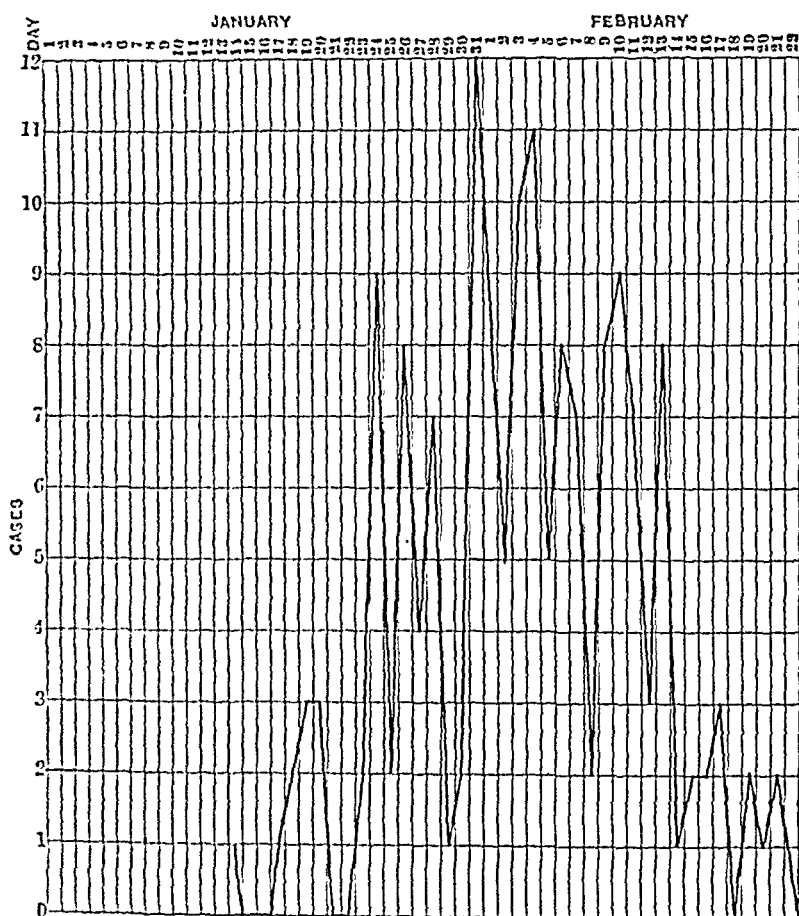
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IN the epidemic of 1918 a very unusual opportunity was given to study the pulmonary changes from the earliest moment of onset to final changes that resulted in the death of the patient. The result of that work was published in 1919.<sup>1</sup> The main features were briefly an early general pulmonary congestion; a rapid development, the climax often being reached in four days; pneumonia developing frequently twenty-four hours after influenza onset. The pneumonias progressed from the hilus, in almost 50 per cent. of the cases, and in 33 per cent. they progressed from the right base. In the true influenza cases which did not develop into pneumonias the greatest congestion was of the hilus and the mediastinum, with peribronchial thickening. The cases developing into bronchopneumonias and bronchial congestion were very noticeable, rapidly developing into small localized areas of congestion, with true confluent parenchyma congestion following immediately. In some cases there was difficulty in differentiating bronchopneumonias from lobar pneumonias. In the majority of cases the early dilatation of the heart and the high position and increased dome shape of the diaphragm were marked features. In the series of 91 cases studied 52 were cases of bronchopneumonia and only 4 of lobar pneumonia. The radiographic appearances were consistent and typical.

In view of the fact that a study had been made in 1918 it was thought of sufficient interest and importance to attempt a study of the present epidemic. No true comparison, of course, can be made. The conditions under which this study was carried out were far from ideal, the class of patients entirely different, control and coöperation lacking, clinical data insufficient, autopsy corroboration unobtainable, so that in many ways the present study should in no way compare with the results obtained in 1918. There are, however, certain very definite changes observed and results obtained which are significant, and to a certain extent they compare with the general mild clinical and epidemiological features observed in the present epidemic. Moreover the radiographic findings are comparable and for the sake of simplicity the cases studied have been put into purely arbitrary groups, based solely on the changes observed in the radio-

<sup>1</sup> Honeij, James A.: *Influenza and Bronchopneumonia: A Study of the Epidemic from a Roentzenological Point of View.*

grams. The following general information is given regarding the number, source and type of cases from which our series were obtained:



GROUP I. *Lobar Pneumonia*. This group consists of 6 cases of definite lobar pneumonia. There is some congestion throughout both lungs. The only significant feature is the typical localized area of density. The base of the process is at the periphery and its apex at the hilus. In no case does the process occupy more than one lobe. In all 6 cases the diaphragm is high and the right auricle of the heart is dilated. In 2 cases there is a question of pulmonary tuberculosis—in all a definite history of influenza. Of these 6 cases 2 died and 4 recovered.

GROUP II. *Diffuse Light Probable Bronchopneumonias*. This group consists of 14 cases. The radiographic examination shows, without exception, a unilateral pulmonary process. In a few cases it was accompanied with congestion on the other side. In the majority of cases the density seemed greatest around the hilus and

bases. Although the lungs were increased in density there were areas in which the density is more or less localized, but of a light, diffuse nature, and in most cases quite extensive. Although these cases were chosen from the daily clinic, with no intention of selection they presented the same features above described. It was impossible to definitely state whether they were lobular or lobar pneumonias. In the more extensive processes, with one exception, the heart and diaphragm and other detailed pulmonary structures could be seen through the density. In the majority, bronchial markings were increased. There was no consistent change in either mediastinum, diaphragm or heart, although in the majority of cases there was some dilatation of the right auricle and pulmonic area of the heart. The diaphragm in a few cases was rather high in position. In a few cases emphysema was present. Of this group 4 died and 8 recovered.

GROUP III. *Diffuse Light Pneumonias*. This group consists of 12 cases. It is comparable to Group II as far as the general light diffuse density is concerned. All the cases presented a unilateral process at the base with one exception, which was bilateral; 5 occurred at the left base and 7 at the right base. There is no evidence that these are bronchopneumonias. The density is sufficient to slightly obscure the outline of heart and diaphragm, but definite pulmonary markings are discernible through the density. This density was not demarcated and gradually faded out. There were no striking associated features in either mediastinum, heart or diaphragm. In some of the cases the mediastinum is slightly increased in width and in only 2 cases are the borders slightly obscured by the mediastinal density. In 3 cases the diaphragm is somewhat high but not exceptionally so if compared with the size of the thorax. Two of these cases died and 9 recovered.

GROUP IV. *Diffuse Congestion*. This group consists of 5 cases. It is a group that was originally described as diffuse congestion. The only feature of significance was an increase in the width of the mediastinum and considerable increase in density along the peripheral borders of the lungs in 3 out of 5 cases. All 5 cases recovered.

GROUP V. *Typical Bronchopneumonias*. This group consists of 6 cases. The outstanding feature is the irregular, patchy density, peribronchial in type, extending from the hilus outward in all directions. In general there is very little pulmonary congestion outside of the areas described—largely unilateral in type. The associated changes are quite marked. The diaphragm is high; the mediastinum is obscured and increased in width, with the exception of 1 case. There is some dilatation of the auricle and pulmonic area of the heart. In 1 case this is slight.

This group was taken as a contrast to Group I and Group III, which are the two important groups. Two of this group died and four recovered.

Of the 43 cases in the five groups, 40 were charted and an attempt made to compare the clinical with the radiographic information. The following information was sought: The age, sex, previous respiratory diseases, duration of illness before radiographic examination, clinical symptoms, pulse, temperature, physical signs, both front and back, clinical diagnosis, blood examination, pneumococci type determination and end-results. These results were not compared until the cases had been grouped radiographically, studied and recorded. The result of the charted cases is as follows: The ages of the patients were between nineteen and sixty years, the greatest number, more than one-half, were between twenty-five and thirty-five years of age. There were twenty-five male and fifteen female patients. Except for 3 cases, none of the patients gave a history of having had influenza previously. The duration of the disease previous to radiographic examination was from one to twenty-three days. The typical clinical symptoms of chills, fever, headaches and "pains all over" prevailed in practically all cases. The highest temperatures occurred in Groups I and II. In Group III no temperature exceeded 103°. The pulse was over 100 in all but 4 cases. The physical examination was of interest, as in 9 cases only were pulmonary changes recorded in front of the chest, while in the majority the physical signs were at the back and bases. There was no predominating physical sign nor did the physical findings in type differ from the previous epidemic. The clinical diagnosis was recorded in most cases after radiographic examination, so that no comparison can be made. The blood examination gave no information of value so far as the grouping of our cases is concerned. It depends on too many diverse factors to draw any group comparison. The white blood cells varied in number from 5 to 30,000. The pneumococci type determination bears no relation apparently to the type, degree or extent of radiographic changes so far as the groups are concerned. In Type IV, however, 9 cases recovered and 6 died, this being the greatest number.

The end-results in this group of 40 cases showed that 12 cases died, 27 recovered and 1 was not recorded. In Group I, 2 died and 4 recovered. In Group II, 4 died and 8 recovered. In Group III, 2 died and 9 recovered. In Group IV, all recovered, and in Group V, 2 died and 4 recovered. Three cases were complicated, of which 2 died.

Although no definite conclusions are obtained from this analysis there are several interesting points to be noted if compared with the radiographic findings. In Groups III and IV, which are the groups that radiographically are less serious than the other groups, the temperatures were lower and end-results better, with fewer fatal cases, than in any of the other groups. In the majority of cases the physical findings at the back and bases gave no indication of the type or position of the pulmonary density seen on the radio-

grams. These physical signs, however, simply indicated the general congestion, which was most notable at the bases and seen radiographically in all cases. It is interesting to note that only three of the cases gave a previous history of having had influenza.

From a radiographic point of view the significant features of the findings in this epidemic as compared with the findings in the previous epidemic can be stated briefly as follows: In Groups II, III and IV the pulmonary congestion was lighter and more diffuse; although more or less localized, it occupied a large lung area, with less associated cardiac and diaphragm reaction than in the cases in 1918. There was less congestion of the hilus, peribronchial, mediastinal tissues and tracheobronchial glands. This diffuse, light pulmonary congestion bore no relation to the duration of the disease in that our cases were radiographed anywhere from one to twenty-three days after admittance.

There is here no evidence that our cases were typically bronchial or lobar in character which was such a specialized feature in 1918. The process developed slower and in no such well-defined manner, as in the cases of the previous epidemic. The general pulmonary congestion in all 52 cases was no different from that previously seen. These facts suggest, therefore, that in the majority of cases we were dealing with a pulmonary infection that was less severe than the infection of 1918.

Total cases 138—of 124 cases age incidence as follows:

—20	20-25	25-30	30-40	40-50	Over 50
10	28	31	30	15	10

Duration of disease at entrance:

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	20	21
Cases	9	37	17	22	14	16	15	6	5	5	1	2	..	4	..	..	1	1

History of previous influenza:

Total cases 138—12 cases or 8.7 per cent.:

Clinical Diagnosis:

Bronchitis or influenza.	Bronchopneumonia.	Lobar pneumonia.	Empyema.
68	79	11	3

Type determination—58 cases:

Type I	II	III	IV	Strep. viridans	Strep. hemolyticus	Strep. mucosus
4	..	9	31	3	8	3

Mortality—161 cases: 46 died, or 28.57 per cent., or 285 per thousand.

From these 138 cases 52 had radiograms made and studied. These cases were divided into five groups according to the changes



observed radiographically. They were compared with a group of 9 cases of influenza so that in all cases there would be a so-called standard for comparison. The description of this group is as follows:

**Influenza Group Used as a Control in Studying a Group of Pulmonary Congestion Cases and Changes Consistent with Early Bronchopneumonia or Diffuse Pneumonia.** Examination of the radiograms of 9 cases shows more or less the same changes. The lungs throughout are slightly increased in density. In the majority of cases there is a slight increase in the width of the mediastinum. The hilus is rather large, increased in density and of very irregular outline. Radiating from the hilus the peribronchial thickening is quite marked. There are no marked diaphragmatic or cardiac reactions. In all the cases the pulmonic area of the heart is dilated but consistent with the degree of pulmonary congestion. There is no marked elevation of the ribs. In a few cases there is some emphysema at the bases and in others an emphysema which might be called compensatory in type.

Of this group three are males and six females. All recovered.

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## OBSERVATIONS ON THE LATEST (1920) RECRUDESCENCE OF INFLUENZA: A DETAILED CLINICAL STUDY OF 100 CONSECUTIVE CASES.

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DURING the first two weeks of January of this year (1920) cases of respiratory infections resembling clinically the ailment known as influenza or la grippe became prevalent in this city. During the third week of the month the cases became more numerous. Instances of several individuals in the same household being affected were quite common and severe infections resembling the fatal cases of the last epidemic made their appearance. Special wards for influenza patients were opened in the Waterbury Hospital and the following observations are the results of the laboratory and clinical studies of 100 consecutive cases treated. On the whole, these cases represent the majority of the worst patients during the epidemic, although a few of our cases were comparatively mild.

The object of this paper is to record the clinical features of the epidemic, also the bacteriologic findings, and to present the logical deductions that one may draw from them.

**Analysis of the Cases.** Of the 100 patients treated, 49 were males and 51 were females. The age incidence was as follows:

Below 5 years	4
Between 5 and 10 years	2
"    10 and 20	6
"    20 and 30	35
"    30 and 40	37
"    40 and 50	8
"    50 and 60	4
Above 60 years	4
	<hr/> 100

**Date of onset:** The onset arranged by weeks was as follows:

January 4 to 10	6
11 to 17	15
18 to 24	34
25 to 31	24
February 1 to 7	13
8 to 14	6
15 to 21	2
	<hr/> 100

The rapid rise in the number of cases and also the abrupt subsidence of the epidemic is shown in the accompanying chart (Fig. 1).

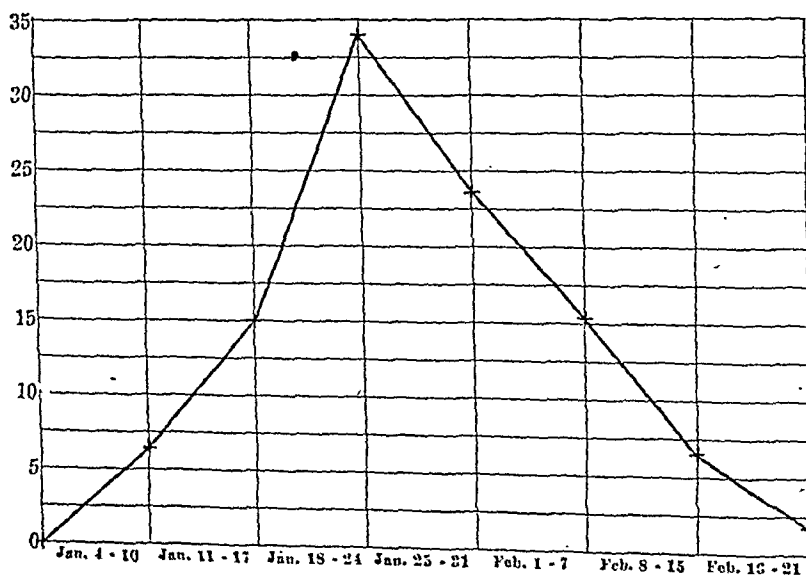


Fig. 1

*Influenza during the Last Epidemic.* In only 2 of the cases (both of which recovered) were we able to elicit a history of having had the influenza during the epidemic of last year. In 1 case the infection was mild, keeping the patient in bed but one day. In the other there was a history of bronchopneumonia of six weeks'

duration. A history of previous attacks of pneumonia was obtained in 4 cases: 1 ten years ago; 2 six years; and 1 three years prior to present admission. In the rest of the patients there was no history of any respiratory affection sufficient to confine them to bed. A history of frequent attacks of rhinitis and "colds" was obtained from a number of the patients, but its frequency was no higher than in 100 other patients similarly questioned.

*Mode of Onset.* Before the patients were confined to bed there was generally some malaise and headache of about twelve to twenty-four hours' duration. Chilliness was present in 95 per cent. of cases. In 12 per cent. of the cases it was very marked—an actual chill—from the very beginning. In 76 per cent. of the cases that subsequently developed pneumonia a renewed chill of marked severity ushered in the beginning of consolidation. Sneezing was not conspicuous during the epidemic (3 per cent.), while rhinitis and "a cold in the head" were present in 14 per cent. of cases. In the majority of instances the illness commenced with general malaise, headache, chilliness, pain in the back and prostration. Cough was an early and distressing symptom in 74 per cent. of cases.

*Clinical Course and Physical Signs.* Of the 100 cases investigated, 48 had marked pneumonic involvement, 18 cases had severe bronchitis, with several small areas of bronchopneumonia; 28 patients had a bronchitis of moderate severity, while 6 other patients had merely a pharyngitis with slight tracheitis.

In 16 cases under our observation we had the opportunity to note the development of pneumonia from its very onset. None of these cases had the abrupt onset that goes with lobar pneumonia. They did not have the severe chill, the sudden rise of temperature and the rapid development of the disease as commonly seen in cases of lobar pneumonia. On the other hand, almost invariably the history obtained from the patient was that of an ordinary cold, with a slight bronchitis. He presented the symptoms of a slight infection. He generally had a dry, hacking, non-productive cough, with some presternal pain. The temperature was usually about 102° F. on the first day and about 102° to 103° F. on the second day. A diurnal variation of temperature was quite marked. If no complications developed the temperature usually came down by lysis and remained normal after four or five days of irregular pyrexia. In the cases complicated by pneumonia the diurnal variation of temperature became less marked, and usually on the fourth to the sixth day of illness the temperature would suddenly rise 2° or 3°, generally preceded or accompanied by a marked chill. At this time the physical examination of the chest would reveal a small localized area where the rales were finer than elsewhere. Percussion was generally negative at this stage; the breath sounds were very little altered but spoken, and particularly whispered voice was frequently increased over the involved area. The area of involvement when

first observed in these cases was usually small (about the size of a half-dollar) and circumscribed. The most frequent location of the early signs of consolidation was in the upper part of the lower lobes posteriorly (Fig. 2). Gradually the involvement extended, and in the course of two or three days a large part or perhaps an entire lobe of a lung was involved. Involvement of contiguous parts of the lung was gradual. Neighboring lobes were frequently involved four to six days after the first evidence of consolidation. Similarly, areas of bronchopneumonia or evidences of lobar pneumonia would appear on the opposite side of the chest many days after the appearance of the primary signs.

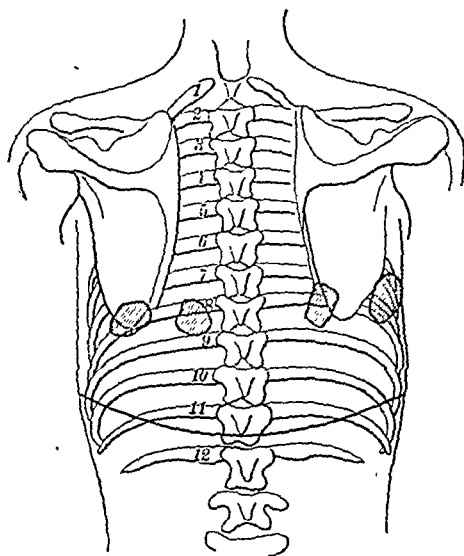


FIG. 2.—Areas where the earliest signs of consolidation were most frequently observed.

Five fatal cases of pneumonia were seen during the epidemic, which simulated very closely the fulminating influenza pneumonia cases seen last year. They had the mottled cyanosis when first seen. Epistaxis was profuse and prostration marked. The pulse was comparatively slow and the leukocytosis was either normal or else a leukopenia was present. The postmortem findings were those of large areas of bronchopneumonia in both lungs, with generally a lobar involvement of one or more lobes. Bacteriologically these cases were mixed infections. The influenza bacillus was found in two such cases, one in combination with the pneumococcus and the other with the streptococcus. In the rest of the cases the pneumococcus and streptococcus were isolated.

Considering the symptoms of the other cases we found several features predominating, which accentuated certain differences from a similar series of pneumococcus pneumonias.

TABLE I.—TABULATION OF THE BLOOD AND BACTERIOLOGIC FINDINGS IN FORTY-EIGHT CASES OF PNEUMONIA.

No.	Name.	Age.	Sex.	Diagnosis.	Blood.		Throat.		Sputum.		Blood culture.	Group.	Termination.
					White blood cells.	Polynuclears.	Pfeiffer.	Other organisms.	Pfeiffer.	Other organisms.			
1	Mrs. D.	24	F.	Lobar pneumonia, right base	24,000	74	0	Streptococcus; pneumococcus	0	Pneumococcus; streptococcus; M. catarrhalis	Negative	II	Recovered.
2	A. E.	31	F.	Lobar pneumonia, double	24,200	78	+	Pneumococcus	+	Pneumococcus	Pneumococcus	IIa	Recovered.
3	Ford	84	M.	Bronchopneumonia, diffuse	16,400	83	+	Pneumococcus; streptococcus	+	Pneumococcus; streptococcus	.....	II	Recovered.
4	D. McD.	26	M.	Lobar pneumonia, 3 lobes	18,200	94	+	Pneumococcus; streptococcus	+	Pneumococcus; streptococcus; M. catarrhalis	Streptococcus (mucosus)	III	Died.
5	B. B.	30	M.	Lobar pneumonia, 2 lobes, right	33,000	86	0	Pneumococcus; streptococcus	0	Pneumococcus; streptococcus; Friedländer's	Negative	II	Recovered.
6	H. W.	42	M.	Lobar pneumonia, right middle	34,600	82	0	M. catarrhalis; streptococcus	0	Pneumococcus; streptococcus	Negative	II	Recovered.
7	R. P.	23	M.	Lobar pneumonia, right base	29,000	89	+	Streptococcus; staphylococcus	+	Pneumococcus; M. catarrhalis	Negative	II	Recovered.
8	J. R.	41	M.	Lobar pneumonia, double	31,200	86	+	Streptococcus	+	Pneumococcus; M. catarrhalis	Negative	III	Recovered.
9	LaR.	26	F.	Bronchopneumonia, diffuse	12,400	71	..	.....	+	Pneumococcus	Pneumococcus	IV	Died.
10	J. B.	36	M.	Lobar pneumonia, right base	20,600	90	0	Pneumococcus; streptococcus	0	Pneumococcus; streptococcus	Pneumococcus	I	Recovered.
11	Mrs. Day	34	F.	Lobar pneumonia, 3 lobes	...	...	...	.....	0	Pneumococcus; streptococcus	.....	II	Recovered.
12	G. W.	14	F.	Lobar pneumonia, right base	7,800	79	0	0	+	Pneumococcus	.....	IV	Recovered.
13	F. B.	24	M.	Bronchopneumonia, diffuse	21,200	87	0	Streptococcus; staphylococcus	+	Pneumococcus; M. catarrhalis	Negative	II	Recovered.
14	J. Biero	36	M.	Double pneumonia	20,600	90	0	Pneumococcus; streptococcus	0	Pneumococcus; streptococcus	Pneumococcus	I	Recovered.
15	E. G.	29	M.	Lobar pneumonia, left lung	13,200	77	..	.....	+	Streptococcus	Pfeiffer	...	Died.
16	Mrs. B.	56	F.	Bronchopneumonia, diffuse	22,000	87	+	Streptococcus	+	Streptococcus; pneumococcus	.....	...	Recovered.
17	Waz.	36	M.	Lobar pneumonia, left base	15,000	81	0	Pneumococcus; streptococcus	+	Pneumococcus	Negative	IIa	Recovered.
18	De F.	..	F.	Lobar pneumonia, right middle	24,200	87	0	Streptococcus; staphylococcus	0	Streptococcus; pneumococcus	.....	IV	Recovered.
19	H. S.	3	F.	Lobar pneumonia, left lung	18,200	74	..	.....	..	Pneumococcus	Negative	III	Died.
20	M. G.	24	M.	Lobar pneumonia, left base	16,600	72	..	.....	+	Pneumococcus	.....	III	Recovered.
21	Mrs. R.	..	F.	Lobar pneumonia, left base	18,200	86	..	.....	0	Pneumococcus; streptococcus	.....	III	Recovered.

No.	Name	Age	Sex	Diagnosis	Weight	Temp.	Pulse	Respiration	Condition	Microbes	Result	Final
22	Mrs. W.	32	M.	Bronchopneumonia, diffuse	14,000	87	0	0	Streptococcus; streptococcus; Staphylococcus; pneumococcus; streptococcus	Pneumococcus	Recovered.	IV
23	D. M.	16	M.	Lobar pneumonia, right upper	8,500	74	+	+	Streptococcus; pneumococcus; streptococcus	Pneumococcus	Recovered.	IV
24	Mrs. E.	35	F.	Lobar pneumonia, left base	9,200	88	+	+	Streptococcus; Streptococcus	Pneumococcus	Died.	II
25	E. P.	..	M.	Lobar pneumonia, left base	4,300	73	+	+	Streptococcus	Streptococcus; Streptococcus	Recovered.	..
26	Mr. H.	32	M.	Lobar pneumonia, right upper	8,100	50	..	..	Streptococcus	Pneumococcus	Died.	..
27	Mrs. A.	29	F.	Lobar pneumonia, right lower; middle	9,200	74	+	+	Streptococcus	Pneumococcus	Recovered.	I
28	Miss W.	23	F.	Lobar pneumonia, left base	9,200	72	+	+	Streptococcus	Pneumococcus; B. fusiformis; M. catarrhalis; Streptococcus; M. catarrhalis; Streptococcus; Streptococcus; Streptococcus	Died.	..
29	J. K.	..	M.	Double pneumonia	5,000	50	..	..	Streptococcus	Pneumococcus; Streptococcus	Recovered.	Neg.
30	A. M.	..	M.	Double pneumonia	9,600	86	+	+	Streptococcus; streptococcus; Streptococcus	Pneumococcus; Streptococcus	Recovered.	IV
31	McI.	..	M.	Double pneumonia	5,600	77	0	0	Streptococcus	Pneumococcus	Died.	..
32	F. Z.	..	M.	Lobar pneumonia, right base	6,200	78	..	..	Streptococcus	Pneumococcus	Recovered.	..
33	Mrs. Du.	..	F.	Lobar pneumonia, left base	14,600	83	..	..	Streptococcus	Pneumococcus; Streptococcus; Friedländer	Died.	III
34	H. H.	64	M.	Lobar pneumonia, rt. lower; middle	14,800	85	..	..	Streptococcus	Pneumococcus; Streptococcus; Friedländer	Recovered.	IV
35	Mrs. H.	..	F.	Bronchopneumonia, diffuse	10,600	83	..	..	Streptococcus	Pneumococcus; Streptococcus; Friedländer	Recovered.	Neg.
36	Miss N.	..	F.	Bronchopneumonia, diffuse	4,200	63	+	+	Streptococcus	Pneumococcus; Streptococcus; M. catarrhalis	Recovered.	..
37	Mrs. E.	..	F.	Lobar pneumonia, left base	5,000	57	0	0	Streptococcus; M. catarrhalis	Streptococcus; staphylococcus	Recovered.	..
38	Mrs. M.	..	F.	Lobar pneumonia, right base	11,800	81	..	..	Streptococcus	Pneumococcus	Died.	..
39	Baby R.	9 mos.	F.	Bronchopneumonia, diffuse	31,200	94	0	0	Streptococcus	Streptococcus M. catarrhalis	Recovered.	..
40	J. M.	..	M.	Lobar pneumonia, right middle	5,000	52	+	+	Pneumococcus	Pneumococcus	Died.	III
41	F. S.	29	M.	Bronchopneumonia, diffuse	5,700	63	0	0	Streptococcus; Friedländer	Pneumococcus Friedländer	Recovered.	..
42	Mr. B.	..	M.	Bronchopneumonia, diffuse	24,200	61	..	..	Streptococcus	Pneumococcus; Streptococcus	Died.	..
43	Mrs. S.	..	F.	Bronchopneumonia, diffuse	16,200	81	0	0	Pneumococcus; Streptococcus	Pneumococcus; Streptococcus	Recovered.	II
44	Baby D.	..	F.	Lobar pneumonia, left lung	..	..	..	..	Streptococcus	Pneumococcus	Recovered.	..
45	C. A.	..	M.	Lobar pneumonia, high base	19,200	84	0	0	Pneumococcus; streptococcus; Streptococcus; staphylococcus; Pneumococcus; streptococcus	Pneumococcus	Recovered.	IV
46	J. C.	35	M.	Bronchopneumonia, diffuse	7,900	75	+	+	Streptococcus; streptococcus; Streptococcus	Pneumococcus; M. catarrhalis	Recovered.	II
47	B. M.	..	F.	Bronchopneumonia, diffuse	9,100	69	0	0	Streptococcus	Pneumococcus; staphylococcus; Friedländer	Negative.	II
48	A. B.	16	F.	Bronchopneumonia, diffuse	8,100	67	+	+	Streptococcus	Pneumococcus	Recovered.	..

1. *Epistaxis* was a very frequent symptom. It was present to some extent in 64 out of 100 cases studied and in 38 out of the 49 pneumonia cases (80 per cent.). In 12 of the 64 instances of epistaxis it was marked in extent and in 4 of the patients measures had to be taken to control it. It occurred on the first day in 4 cases, on the second in 8, on the third in 21 and between the fourth and eighth in the rest of the cases.

2. *Herpes* was present in only 4 patients and in only 2 of the pneumonia cases (3.8 per cent.).

3. *Leukocytosis* was frequently low and in the cases in which counts above 20,000 were obtained it was not until three to five days of more or less consolidation had elapsed. As will be seen from the records of the blood counts on our pneumonia cases, in a number of instances the total white count remained practically normal throughout the course of the illness. Nevertheless, in the majority of cases some rise of the total white count took place with the onset of consolidation. It varied in extent and frequently was not observed until several days later. In many instances the increase in leukocytes was merely from 2000 to 5000 per c.mm.

4. *Sputum*. While blood-tinged sputum was present in 84 per cent. of the pneumonia cases, rusty and tenacious sputum was present in only 1 case.

5. *Pleuritic pains* were not conspicuous. Only 2 of the patients in this series had sufficient pain to necessitate strapping of the chest.

6. *A diffuse bronchitis* was present in 45 to 48 pneumonia patients (93.6 per cent.) and subcrepitant rales were present and persisted in both apices in twelve of the 100 cases, and in 6 per cent. of the pneumonia cases.

7. *The temperature* came down by crisis in 6 (12.5 per cent.) cases and by lysis in 42 (87.5 per cent.).

8. *Menstruation* was unaffected in the majority of cases. The amenorrhea frequently seen in cases of pneumonia was absent in the cases under our observation. In the majority of cases the menstruation was regular, but in 6 cases it appeared several days before the usual period, and was accompanied by menorrhagia.

9. *Extensive scaling* of hands and feet was seen in 2 of our pneumonia cases.

*Temperature*. The highest temperature observed in the 100 cases may be tabulated as follows:

Temperature.	No. of cases.
101.0° F. . . . .	12
102.0° F. . . . .	25
103.5° F. . . . .	23
104.5° F. . . . .	29
105.0° F. . . . .	8
106.0° F. . . . .	2
108.0° F. . . . .	1

*Duration.* The length of illness in the 100 cases was as follows:

Less than 7 days . . . . .	32
Between 7 and 10 days . . . . .	31
"    11 and 14 " . . . . .	17
"    15 and 18 " . . . . .	14
Above 18 days . . . . .	6
	<hr/> 100

*Pulse.* The maximum pulse-rate usually varied between 90 to 110. When a rate of above 120 persisted the outcome was generally poor. In one of our cases, a child, aged three years, a pulse-rate of 140 to 160 persisted for three days, with complete recovery. In another patient, with pneumonia, a girl, aged fourteen years, a pulse of 132 to 146, was present at irregular periods during the course of three days, also with complete recovery. In 92 per cent. of our cases in adults, however, a pulse-rate of above 120 that persisted for more than twenty-four hours proved fatal. We have not seen a single case of pneumonia in an adult recover with a pulse-rate of above 140, lasting more than four hours, unless that increase was distinctly due to some temporary excitement.

During the height of the disease no irregularities of the pulse, except *pulsus paradoxicus*, were observed. Irregularities of force and rhythm appeared, with the onset of cardiac failure or vascular paresis and proved fatal in 96 per cent. of such cases. During or after the crisis intermittences and extrasystoles were noted in 6 cases of pneumonia (12.5 per cent.).

*Blood-pressure.* It was below 100 systolic in 14 of the 100 cases; between 100 and 110 in 40 per cent.; between 110 and 120 in 28 per cent.; and between 120 and 140 in 18 per cent.

When the pulse-rate per minute was markedly above that of the systolic blood-pressure expressed in millimeters of mercury the outcome was generally poor, but a variation of ten to twenty points was observed, frequently with no special influence on the outcome.

On the whole the rise in the pulse-rate was a much better indication for prognosis than the fall in blood-pressure. Several of our cases that recovered had a systolic blood-pressure of 86 to 90 during the height of the disease, while a number of our cases died when the pulse-rate rose above 120 even though the systolic pressure was between 130 and 140 at the same time.

*Laboratory Findings. Blood.* One hundred and twenty-eight blood examinations were made upon 88 of the 100 cases. The hemoglobin and red-cell count showed no special changes. 128 white blood counts were made. They were below 5000 sixteen times; between 5 and 10,000 fifty-three times; between 10 and



20,000 forty-four times and above 20,000 fifteen times. In the pneumonia cases the white blood counts were as follows:

	Cases.	Per cent.
Below 10,000 . . . . .	20	43.6
Between 11,000 and 15,000 . . . . .	9	19.5
" 16,000 and 20,000 . . . . .	7	15.5
Above 20,000 . . . . .	10	21.4
	<hr/> 46	<hr/> 100.0

In the majority of the cases that were not complicated by pneumonia the white blood count was generally between 5 to 10,000. Of the 16 counts where the white blood cells were less than 5000 all but one were in uncomplicated cases. In 18 cases not included in the pneumonia tabulation the blood count was between 10 to 20,000. They were all cases of extensive bronchitis and a number of them had several areas of bronchopneumonia.

*Otitis media* was generally accompanied by an increase of the total white and by a rise of the polynuclears. Empyema was accompanied by a temporary increase of the white cells. If the disease was of more than one week's duration the total white count generally dropped while the polynuclears and especially the large mononuclears and transitionals became increased.

The white count did not prove of great value as a prognostic aid in our pneumonia cases. In our 12 fatal cases, 4 white counts were below 10,000, 5 between 10 and 15,000 and 3 were between 18 and 24,000. Since 20 of our pneumonia patients had a white count of less than 10,000, it would indicate a mortality of 20 per cent. of these cases, while the mortality was 25 per cent. of the series.

Differential determinations of the leukocytes were also made 128 times upon 88 of the 100 cases. The polynuclears were below 75 sixty-six times and above 75 sixty-two. The lymphocytes were below 25 eighty-three times and above 25 forty-five. The mononuclears and other elements were not altered to any noticeable extent.

*Throat Smears.* Throat smears were taken in 73 cases. The bacillus of influenza was found in 42 of the cases (57.5 per cent.). In the majority of cases it was found in combination with the pneumococcus, streptococcus and *Micrococcus catarrhalis*. In the pneumonia cases the influenza bacillus was found in 16 out of 35 cases examined (45.7 per cent.). It was in combination with the pneumococcus in 9 of these. In the rest, streptococci, staphylococci and *Micrococcus catarrhalis* were found.

*Sputum.* The *Bacillus influenzae* was found in the sputum of 49 of 78 patients examined (62.8 per cent.). In our pneumonia cases the Pfeiffer bacillus was isolated from the sputum of 27 of the 41 cases examined (63.4 per cent.). In 23 of these instances the

pneumococcus was also found. In the remaining 4 cases the streptococcus and the Friedlaender bacillus were also isolated. In 37 cases uncomplicated by pneumonia the bacillus of Pfeiffer was isolated from the sputum 22 times (60 per cent.). It will hence be seen the frequency of Pfeiffer's bacillus was about the same in the pneumonias as in the uncomplicated cases.

Pneumococcus groupings were done in 30 of the pneumonia cases, with the following results:

			Per cent.
Group I	2		6.65
" II	11		36.80
" II <sub>a</sub>	2		6.65
" III	7		23.30
" IV	8		26.60
	<hr/> 30		<hr/> 100.00

Three patients with Group II and the same number with Group III pneumococcus died, also two other patients with organisms belonging to Group IV.

Group precipitins in the urine were performed on 25 of the pneumonia patients, with the following results:

	No.	Per cent.
Group I	1	4.0
" II	8	32.0
" III	5	20.0
" IV	0	0.0
Negative	11	44.0
	<hr/> 25	<hr/> 100.0

*Urine.* A faint trace of albumin was found during some period of the illness in 59 of the 100 cases. It was present in 46 out of the 48 cases of pneumonia. In the majority of instances it was undoubtedly a febrile albuminuria. With the subsidence of the fever the albumin entirely disappeared. A moderate cloud of albumin was found in 16 cases, a heavy cloud in 7 and a very heavy cloud in 2 of the cases.

Occasional hyaline casts were found in 14 cases, and like the faint trace of albumin were of no special significance.

In 10 out of the 12 fatal cases there was a heavy cloud of albumin and numerous hyaline and granular casts several days prior to the termination. In some of the cases there was a marked albuminuria upon admission to the hospital, and it was therefore impossible to determine whether the albuminuria was distinctly a complication or whether the patient was suffering from chronic nephritis prior to the present illness. In 5 of the fatal cases we were able to note its first appearance. In 1 it appeared on the third day of the illness while in the other 4 it made its appearance two to four days prior to death and was accompanied by cyanosis and other signs of cardiac decompensation and vascular paresis.

Of the 16 cases in this series, with moderate clouds of albumin, 2 died (12.5 per cent.) and 14 (87.5 per cent.) recovered. The 7 cases with the heavy cloud and the 2 with the very heavy cloud all terminated fatally.

Hence it will be seen that in the series of cases that a heavy cloud of albumin and the presence of many casts were an indication of profound illness and of poor prognostic omen.

Acetone was found in 8 cases, but it was always associated with either starvation or repeated vomiting. No definite acidosis referable to disease was demonstrated in our cases. No increase of *indican* was found.

**Complications.** 1. Otitis media was a complication in 4 of the 100 cases. It developed rather late in all cases (tenth to eighteenth day). Two of these patients had bronchopneumonia, one lobar pneumonia and the fourth had only bronchitis.

2. Empyema was a complication in 2 cases. In one it was demonstrated on the twelfth day of the illness and in the other on the twenty-eighth. In 1 case the pneumococcus was isolated from the pus while in the other streptococcus was found.

3. Pleurisy with effusions was present in 2 cases. In both the streptococcus was found. One case ended fatally before pus formation took place. In the other spontaneous resolution took place, with an uneventful recovery.

4. Orbital cellulitis was a complication in one case. There was a very marked protrusion of the eyeball with extensive edema of both eyelids. The temperature rose to 107° F. one day, but, on the whole, the temperature was low and the pulse slow. There was no leukocytosis evident in this case from the complication. An otitis media with a profuse purulent discharge was present on the same side. The orbital cellulitis responded to constant wet dressings, with a good recovery.

5. Nephritis to a marked degree as evidenced by a heavy cloud of albumin and numerous hyaline and granular casts was found in 12 cases, 10 of which terminated fatally.

6. Pregnancy was a complication present in 7 of the cases. Two had influenza bronchitis (1 with pleurisy) and 5 had lobar pneumonia of one or more lobes. One of the patients developed influenza complicated by lobar pneumonia during the puerperium following the spontaneous miscarriage of a six months fetus. She made a slow but complete recovery. Out of the 5 patients with lobar pneumonia in the eighth month of pregnancy 4 died (80 per cent.). They all had premature labor. Two children lived and two were stillborn. The patient who recovered gave birth to a stillborn child. Both patients with the influenza bronchitis recovered. One gave birth about two weeks prematurely, while in the other case the influenza had no untoward influence upon the pregnancy.

TABLE II.—TABULATION OF THE TWELVE FATAL PNEUMONIA CASES.

No.	Name.	Age.	Sex.	Diagnosis.	Complication.	Blood-pressure.	Urine.		Sputum.		Group.	Blood.		Blood cultures.
							Albu- min.	Casts.	Pfeiffer.	Other organisms.		White blood cells.	Polynu- clears.	
1	D. M.	26	M.	Lobar pneumonia	.....	$\frac{124}{70}$	++	++	0	Friedländer's; M. catarrhalis; pneumococcus	III	18,700	88	Streptococcus.
2	Mat.	36	F.	Lobar pneumonia	Pregnancy	$\frac{136}{80}$	+	+	-	.....	...	11,800	81	
3	L. R.	26	F.	Lobar pneumonia	Pregnancy	$\frac{100}{54}$	+	0	+	Pneumococcus	IV	12,400	80	Pneumococcus.
4	Bos.	64	M.	Bronchopneumonia	Cardiorenal	$\frac{132}{74}$	++	++	-	.....	...	24,200	61	
5	B.	32	M.	Bronchopneumonia	Pleurisy with effusion	$\frac{100}{74}$	++	++	+	Pneumococcus; streptococcus	IV	7,800	79	Pneumococcus.
6	A.	29	F.	Lobar pneumonia	Hyperthyroid	$\frac{100}{64}$	++	+	-	.....	...	9,200	74	
7	E. G.	34	M.	Lobar pneumonia	.....	$\frac{116}{50}$	+	0	+	0	...	13,200	77	Pfeiffer's bacillus.
8	H. S.	3	F.	Lobar pneumonia	.....	...	++	+	0	Pneumococcus	III	18,200	74	Pneumococcus.
9	J. K.	48	M.	Lobar pneumonia	Nephritis	$\frac{108}{70}$	+++	+	0	Streptococcus; M. catarrhalis	...	5,000	50	
10	E.	34	F.	Lobar pneumonia	Nephritis	$\frac{116}{80}$	+++	++	0	Pneumococcus	II	9,200	88	Pneumococcus.
11	H. H.	64	M.	Lobar pneumonia	Nephritis	$\frac{140}{82}$	+++	+	0	Pneumococcus; Friedländer's	III	14,600	82	Pneumococcus
12	J. M.	63	M.	Bronchopneumonia	Arteriosclerosis	$\frac{132}{84}$	+++	++	+	Pneumococcus	III	5,000	52	Pneumococcus

Other complications (encephalitis, phlebitis, etc.) were seen during the epidemic, but as they were not complications of the 100 cases here considered we shall not include them in this paper.

**Termination.** Twelve of the 100 cases terminated fatally; all of these had pneumonia. Four of the cases were complicated by pregnancy. In 10 of the 12 fatal cases evidence of a marked nephritis was present. In 4 of the cases just mentioned a chronic nephritis was present from the onset of the present illness. In the other cases death evidently took place because of toxemia with either cardiac failure or vascular paresis. A tabulation of the fatal cases is included (Table II).

**Summary.** 1. One hundred consecutive cases of influenza were analyzed. Of these 48 had lobar pneumonia and 18 cases had extensive bronchitis, with several areas of bronchopneumonia.

2. Of these 100 cases studied only 2 gave a history of having had influenza during the 1918 epidemic.

3. The bacillus of Pfeiffer was isolated from the throat cultures of 57 per cent. of cases examined and in the sputum of 62 per cent. of cases.

4. In the pneumonia cases the incidence of the bacillus of Pfeiffer in the throat and sputum was about the same as in the uncomplicated cases.

5. The cases of pneumonia differed from a similar series of pneumococcus pneumonias by:

- (a) Slow onset.
- (b) Frequency of epistaxis.
- (c) Infrequency of herpes.
- (d) Infrequency of rusty sputum.
- (e) Low leukocytosis.
- (f) Infrequency of pleuritic pain.
- (g) Frequency of extensive generalized bronchitis.
- (h) Defervescence by lysis (87.5 per cent.).
- (i) Frequency of menorrhagia.

6. Albuminuria was common in this series of cases and an abundance of albumin and casts proved fatal in the majority of instances.

7. The pulse-rate proved of better prognostic aid than the blood-pressure determinations.

8. The study of the leukocytic count did not prove of great prognostic aid.

9. The majority of our pneumonia cases were of Types II, III and IV.

10. Twelve of the 100 cases ended fatally. All had pneumonia (25 per cent. mortality).

**Conclusions.** The rapid mode of spread and the numerous instances in which several members in the same household were simultaneously affected justify the opinion that the infection was epidemic in character. The prostration, headache, pain in the

back, the epistaxis, the normal leukocytosis, seem to point clinically that the infections were cases of influenza or *la grippe*. The finding of the bacillus of Pfeiffer in the throat smears of 57 per cent. of cases examined and in the sputum of 62 per cent. and in the blood culture of one case add a great deal of weight to this conclusion. The study of the sputum and the blood cultures in our pneumonia cases, as also the clinical development and prognosis, lead us to the conclusion that in the majority of instances the bacillus of Pfeiffer was to a greater or lesser extent responsible for the pneumonic consolidation either by occurring in combination with the pneumococcus and allied organisms or else by leaving a *Locus minoris resistentiæ* in the lungs for the invasion of the pneumococcus and streptococcus.

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### REPORT OF A CASE OF EXTRADURAL AND SUBDURAL ABSCESS FOLLOWING SUPPURATING FRONTAL SINUSITIS AND OSTEOMYELITIS OF THE FRONTAL BONE.

BY JOSEPH H. BRYAN, M.D.,

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ON May 6, 1919, L. McG., a fairly well-nourished boy, aged fifteen years, was seen by me in consultation with Dr. Charles L. Billard, his medical attendant, who gave me briefly the following history of the case:

"I was called to see the patient at his home in Waterford, Va., January 13, 1919. On examination I found a distinct swelling over the left front sinus, and pus was to be seen under the middle turbinate in the left nostril. The swelling in the forehead was not detected at this time, because the boy was kept in a dark room on account of the light hurting his eyes. During the previous fall and winter he had been in good health, except for some 'nasal catarrh,' and he had on several occasions complained of headaches, particularly when walking and riding his bicycle. During his present illness he has been running a temperature around 100° or 101°, and it was assumed, because of the prevalence of influenza in the neighborhood, he had an attack of this disease.

"On account of the seriousness of his condition he was brought to Washington the following day and admitted to the Episcopal Eye, Ear and Throat Hospital, and the next day, assisted by Dr. O. A. M. McKimmie, his left frontal sinus was opened. There was a large amount of pus immediately beneath the periosteum, and the anterior wall of the sinus showed a small perforation. Practically all the anterior wall of the sinus was removed, the sinus well curetted and the wound packed with gauze and drained externally. He did very well for a week or two, but there was always a large amount of puru-

lent discharge. At the end of two weeks he developed an abscess of the left upper lid. Because of the presence of this abscess, and because of the large amount of discharge, he was operated upon again January 31, 1919. The wound through the eyebrow was enlarged and the sinus thoroughly exposed. There was considerable granulation tissue present, and a sequestrum of bone was removed from the inner wall of the sinus, leaving a perforation into the cranium and exposing the dura over an area of about one-eighth of an inch.

"April 15, owing to a continuance of the discharge, he was operated upon again, with a view of finding some diseased bone that might be the cause of the continued discharge, but none was found. About this time his right maxillary sinus became infected.

"An interesting occurrence in connection with this case is the fact that after the second operation, on the second or third day, while he was being dressed, a cannula was inserted in the wound and the sinus washed out with a warm boric acid solution. No great pressure of the fluid was used, but about four hours later he complained of severe headache, numbness in the right hand, and there was some thickness of speech. In view of the fact that there was a perforation over the dura it is likely that the pressure of the irrigating fluid was the cause of the symptoms just mentioned."

On examination of the boy, on May 6, I found the whole of the left frontal region markedly swollen, pitting on pressure and bloody, purulent secretion exuding through the fistulous opening at the inner angle of the orbit. There was no headache, temperature normal and the patient expressed himself as feeling well. The situation was considered serious, notwithstanding the general condition of the patient, and another operation was advised and consented to by the parents.

He was sent to the Episcopal Eye, Ear and Throat Hospital, and on the following day, under ether anesthesia, the following operation was done: A free incision extending from the outer angle to the inner angle of the orbit, a vertical incision was then made in the median line for an inch and a half, joining the inner extremity of the previous incision. The flap thus formed of skin and periosteum was detached from the frontal bone as high as the eminence. The periosteum was not firmly attached to the bone and a large quantity of bloody pus and granulation tissue was found beneath it. As far as the eminence the bone was mottled and soft. With a sharp curette the softened bone was removed through the entire diseased area without perforating the inner table. The cavity was then packed with gauze soaked in a solution of dichloramine-T in chlorococane and the margins of the wound left open.

The secretions were so profuse as to require fresh dressings twice a day for a week. They gradually subsided, however, and the wound commenced to show a tendency to heal. The convalescence was a long and tedious one, and it was not until the latter part of July

that the external wound was allowed to close for at least two-thirds of its extent. On account of the profuseness of the discharge that still existed the inner margin of the wound was kept open by gauze-packing. Palpation over the left half of the frontal region gave the impression of firm bony substance beneath the skin, and there was no swelling or pitting on pressure. The secretions continued to flow in considerable quantities, and at one of the dressings, in searching for some diseased bone that might be present and causing the continued discharge, the probe passed into the cranial cavity through the opening in the posterior wall of the sinus. The probe passed up to the vertex of the skull, and on withdrawal the secretions flowed more freely. No diseased bone was detected. The general condition of the patient during this period remained excellent—pulse and temperature normal—and at no time was there any headache or other cerebral symptoms. Wassermann reaction was negative.

During my vacation, in the month of August, the case was cared for by my colleague, Dr. Billard, who kept the wound open and maintained drainage.

On my return in September I found the patient's general condition good. Locally the wound had practically closed, save for the fistulous opening at the inner angle of the orbit, through which the secretions continued to flow in considerable quantity. A probe was introduced, as on a former occasion, through the opening in the posterior wall and could be passed without meeting any resistance to the vertex of the skull. A long cannula was then introduced and a thick, bloody, purulent secretion was evacuated, amounting to about six drams. This was done every other day, with the usual amount of secretion being evacuated. A roentgen-ray examination was then made with the probe *in situ*. The plate showed the probe either in the anterior frontal lobe or between the frontal lobe and skull. Unfortunately this plate has been lost and no illustration can be given. Another roentgen-ray examination was then made after injecting through the sinus opening a 10 per cent. solution of nitrate of thorium. This revealed a large abscess between the skull and the anterior frontal lobe and established the fact that we had a large extradural abscess to deal with. This is brought out very clearly in Fig. 1. Thorium proved a valuable aid in enabling us to decide between a cerebral and an extradural abscess.

September 25. Under ether anesthesia the following operation was done: A vertical incision, extending from the hair-line to the root of the nose, was made joining a transverse incision through the brow from the external to the inner angle of the orbit. The flap thus formed was detached from the bone, leaving a full exposure of the left half of the frontal bone. The periosteum was firmly adherent, and it was noted that the osteomyelitic condition had completely healed, the bone being perfectly firm, showing no degeneration in any part of the largely exposed field. A section of bone about one



inch in diameter, commencing at the median line and extending outward on a line with the eminence, was removed, exposing a large abscess sac just under the frontal bone and external to the dura. This sac was filled with a bloody, purulent secretion which, when drawn off, measured about half an ounce. The walls of the sac were quite thick and lined with granulation tissue. A fistulous tract, about two inches in length, was found extending from the sac to the inner angle of the orbit. After emptying the sac the granulations were gently removed and tincture of iodine applied to its walls. A



FIG. 1

large drainage tube was then inserted and drawn through the fistulous tract to the inner angle of the orbit and the vertical and transverse incisions closed with interrupted sutures.

A bacteriologic examination of the pus from the extradural abscess showed non-hemolytic streptococci in pure culture.

Except for several stitch abscesses in the line of the vertical incision the patient progressed rapidly and was discharged from the hospital in ten days. The abscess was drained by means of a drainage tube, the insertion of a cannula into the sac and by suction. The secretions continued quite profuse for a while, but gradually sub-

sided, and during the early part of December had apparently ceased, when the external opening was allowed to close. I saw him frequently during the remainder of this month and he always expressed himself as feeling well. As there were no local or general symptoms present when examined by me on his weekly visits, I could not but feel that the danger of a relapse had passed.

January 5, 1920. Word was received from his home in Virginia that he was ill with influenza, his physician reporting he had an acute bronchitis and a severe inflammation of the accessory sinuses. He gradually recovered from this illness and again reported for observation at my office February 14. His condition was excellent save for a general pallor of the skin, which was attributed to his recent illness, and he was directed to report again in two weeks.

February 16. An urgent message was received from his mother, saying he was very ill and she was bringing him to Washington. I saw him at six o'clock in the evening and noted the boy was critically ill, with a marked septic appearance, temperature  $103^{\circ}$ , swelling over the left frontal region and complaining of severe headache. I attempted to pass the cannula through the old opening at the inner angle of the orbit, but the parts were too thoroughly healed to admit of its passage. The following morning, his condition being no better, he was sent to the Episcopal Eye, Ear and Throat Hospital, when the following symptoms were noted: a dull apathetic expression, nystagmus of the right eye and twitching of the muscles of the face and nausea. Leukocytosis, 23,000.

Awaiting the arrival of his father the operation was deferred until 8.30 P.M., when a vertical and transverse incision was made through the lines of the previous operation and a flap detached from the whole left half of the frontal bone. The periosteum was firmly attached and the outer table of the bone was found to be healthy. The opening into the abscess sac made at the previous operation had been filled in with new bone formation. A larger segment of bone was removed, bringing into view the sac, which was filled with secretion under great tension. About half an ounce of fluid was removed. Another segment of bone was removed from the above opening to the inner angle of the orbit, bringing into view the fistulous tract leading to the extradural sac. The walls of the sac and the sinus were very thick and indurated. Some necrotic bone was removed from the inner table of the frontal bone at the opening leading to the sinus. As far as the eye could determine there was no break in the walls of the sac or of the sinus leading to it. After cleansing the sac of its contents the walls were cauterized with tincture of iodine and the sinus and sac packed with iodoform gauze, the outer third of the transverse incision sutured and the rest of the wound left open.

February 18. The patient reacted in three hours from the anesthetic, but remained for the rest of the night in a semicomatose state.

Respiration labored and at times cyanosed. Dressings moist from wound drainage. On removal of packing no secretion was present. Wound repacked with plain gauze and outer dressing applied.

February 19. Semicomatose condition continues; retains nourishment; can be temporarily aroused; apparently understands questions but cannot answer. Some loss of motion in the right arm. Wound redressed; no secretion in the sac or fistulous tract. Lumbar puncture. Examination of the spinal fluid: Cell count, 370 per c.mm.; globulin; culture on blood agar, no growth. Seen in consultation with Major H. J. Hayes, U. S. Army.

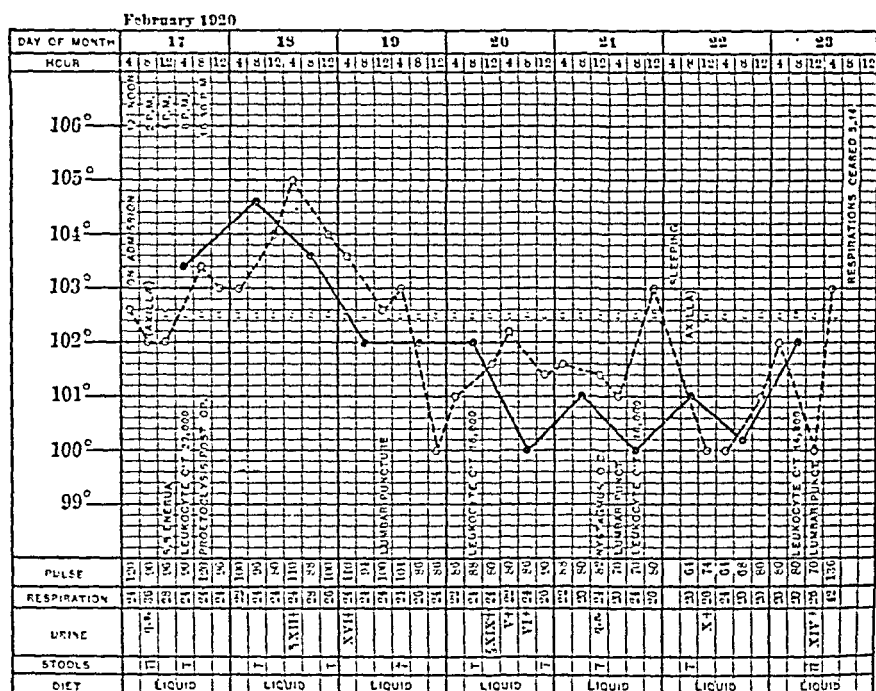


FIG. 2

February 21. Nystagmus of the right eye; twitching of the muscles of the face and mouth; evacuations involuntary. Leukocyte count, 16,000. Lumbar puncture. Examinations of spinal fluid: cell count, 49 per c.mm.; globulin; cultures on blood agar; no growth. 6.30 P.M. nystagmus of the right eye followed by facial muscular twitching, extending to the entire right side, then becoming general. Convulsions from 7 to 1 A.M. relieved by inhalations of chloroform.

February 22. Convulsions continued through the forenoon, when the patient's condition seemed to improve; more rational and taking nourishment better. No change in wound observed at dressing. Eye examination by Dr. Morrison showed nerve ends not swollen.

Veins slightly enlarged; no pressure. Both eyes in good condition. Leukocyte count, 14,000.

February 23. Convulsions, frequent during the night and in the forenoon, controlled by chloroform. Nourishment refused. Growing weaker and died at 5 P.M. For temperature, pulse and respiration see accompanying chart.

*Neurologic Notes by Major H. J. Hayes, U. S. Army.* The patient is in a comatose state and is unable to coöperate in the examination. The pupils are dilated following the use of a mydriatic. Extraocular movements not obtained on account of the mental condition of the patient, but there is no apparent weakness of any of the muscles of the eyes. The tongue is about in the median line and the face a trifle flattened.

*Upper Extremities.* Right side: There is a slight loss of power on this side. Muscle tone about normal. No atrophy and no tremors, except during convulsive seizures. Deep reflexes present and are more active than on the left side. Left-side movement is quite free in all directions. Muscle tone normal. No tremors or atrophy. Deep reflexes present but not as active as those on the right side.

*Lower Extremities.* Right side: Movement of good range in all directions. Muscle tone about normal. No tremors or atrophy. Deep reflexes present and about equal to those on the left side. Babinski negative. Left side: Movement good in all directions. Muscle tone about normal. No tremors or atrophy. Deep reflexes active, and about equal to those on the right side. Babinski negative. Sensory examination negative. Kernig's sign present on both sides.

From the neurologic viewpoint this patient presented several points of interest which, while well known, are of sufficient interest to record: It was noted that he was not able to call the names of objects wanted and that he misplaced words. This condition pointed to a lesion of the temporal lobe or tracts. Unfortunately the paraplesia could not be worked out on account of the patient's mental condition, but this and the convulsive seizures aided to a large extent in the localization of the pathologic process.

The convulsive seizures were of the true Jacksonian type, always starting in the facial muscles, and in a number of instances were confined to the face and forearm of the right side.

Interesting, also, is the relation of the findings in the spinal fluid to the pathology which existed. The first spinal puncture, done about six days before death, showed a cell count of 340 cells and a negative culture. Fluid examined again on the fourth day showed a cell count of 43 cells and a negative culture; and a third examination, two days before death, showed a cell count of 100 and a negative culture. While we realized a meningitis might exist for two or three days and not give more positive findings than those shown in this

case, we are quite certain that we were dealing with a process which was not in free communication with the spinal fluid. The acute condition was so rapid in progress, however, that a decompression was considered inadvisable when it was possible to recognize the condition which existed.

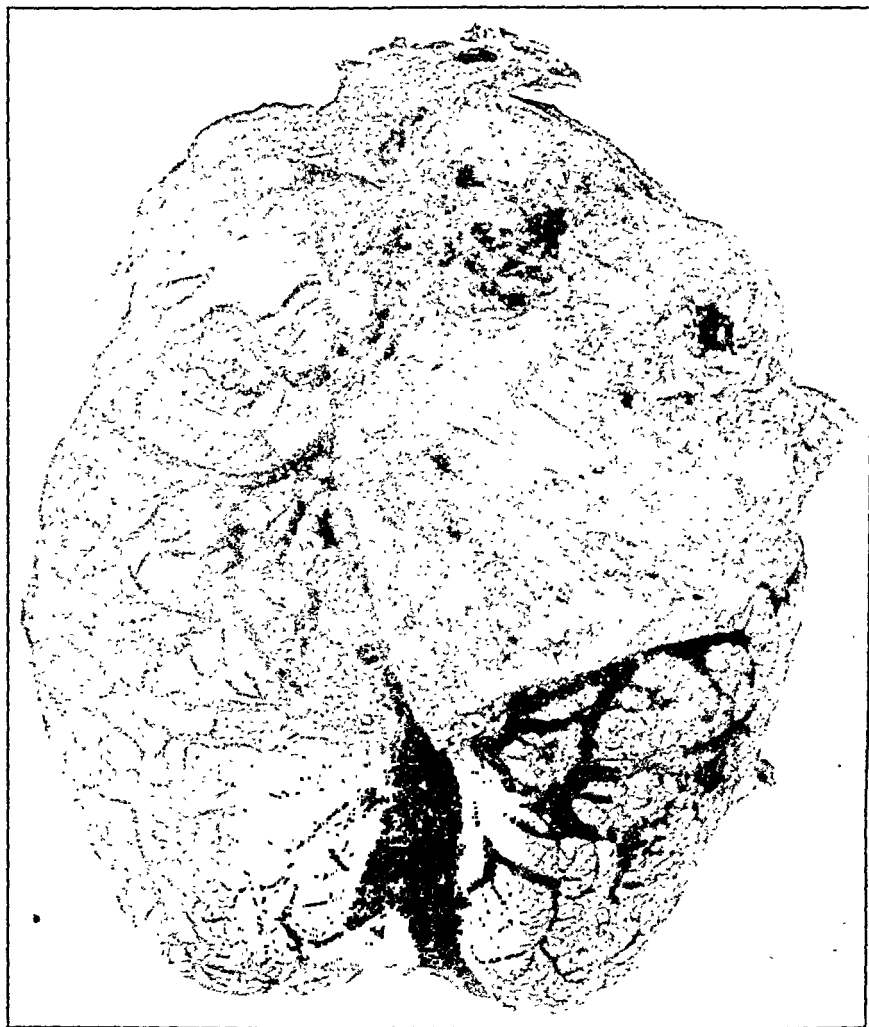


FIG. 3.—Brain. Left dural flap reflected to show under surface; depression in anterior part of left cerebrum.

*Bacteriologic Report by Major Henry J. Nichols, U. S. Army.* The organism found in this case has been identified as the enterococcus. This is undoubtedly the same organism that was found in the previous operation. It is widely distributed and occurs in the mouth, nose and pharynx. It is usually saprophytic but occasionally becomes pathogenic, and cases of meningitis have been due to it as well as cases of bronchopneumonia. This case must be con-

sidered as unusual from the bacteriologic as well as from the surgical viewpoint.

The enterococcus was found frequently in the war wounds in France.

*Report of Autopsy of the Head by Major George R. Callender, U. S. Army.* There is an operation wound just to the left of the median line, extending from the base of the nose upward for about 8 cm. Wound includes the bone to the dura for about 5 cm. The cavity, except the bony wall, was covered by a granulating membrane.

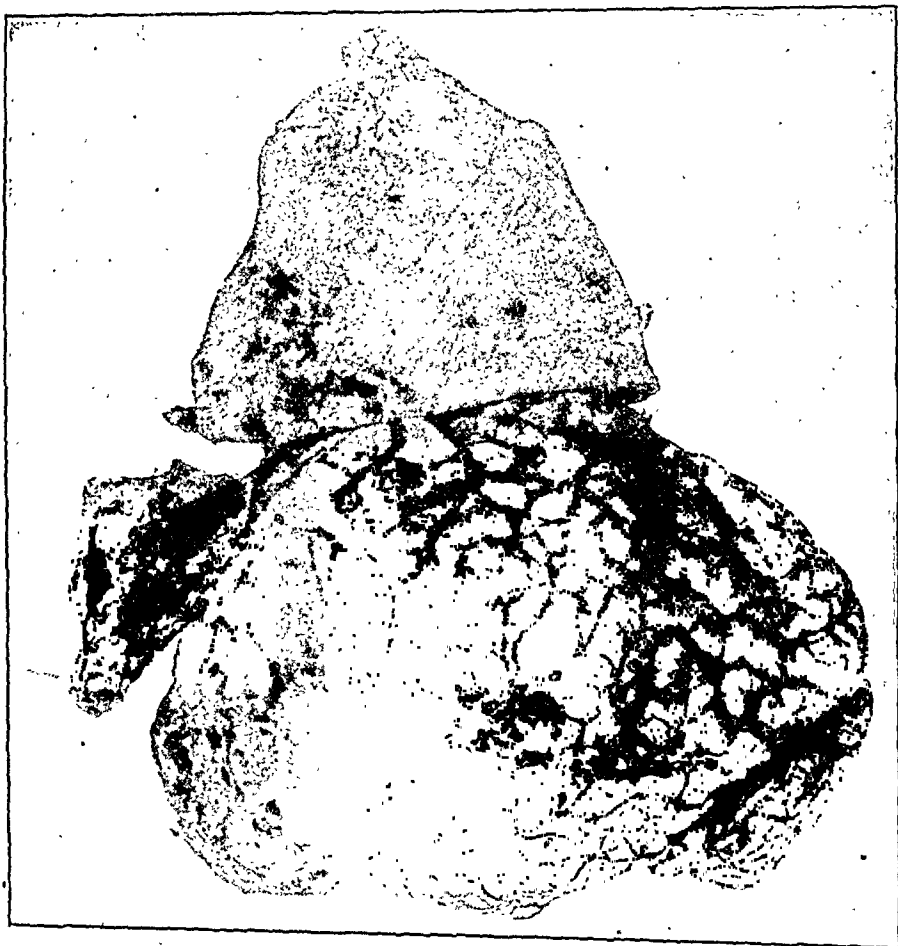


FIG. 4.—Left hemisphere showing subdural abscess and leptomeningitis; extradural abscess sac. Operation wound tract. Dura reflected upward.

Head opened by removing V-shaped section of calvarium. Rather thick yellow pus exudes from saw cuts in the dura of the left hemisphere. Anteriorly there is a thickened area of dura, the floor of the wound cavity measuring 8 x 2 cm. The dura over the left cerebral hemisphere is thickened.

On removing the dura the entire left hemisphere is seen to be covered with a purulent exudate which, over an area roughly 8 x 5

cm., with the center at the junction of the Rolandic with the Sylvian fissure, becomes fibrinous and of a paler color. The under surface of the dura is swollen, granular and injected. The pia-arachnoid is markedly thickened, injected and swollen, obscuring the markedly injected vessels beneath.

The anterior half of the left cerebrum is flattened on the side, and where the thick fibrin forms a mass there is a depression about 1 cm. deep at its center.

The left cerebrum shows marked vascular injection, with some opacity about the vessels in the lower Rolandic area. Frontal sinus involved in operation wound. Ethmoid cells show injected mucosa. Sphenoid antrum filled with yellowish, cloudy fluid. Mucosa injected and swollen.

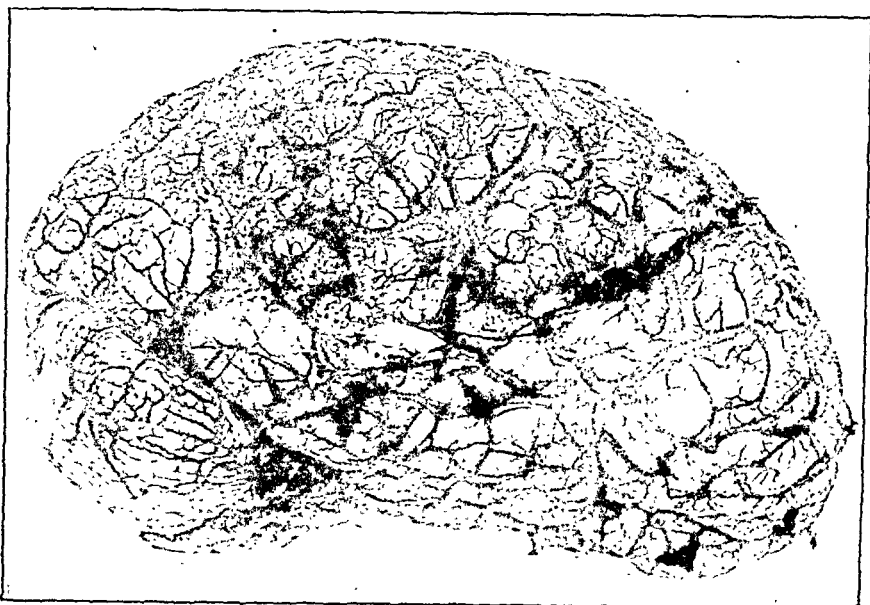


FIG. 5.—Right hemisphere; vascular injection; exudate along vessels in Rolandic area.

Streptococci in short and long chains are abundant in the exudate in and on the surface of the brain, as shown in sections.

The accompanying photographs of the brain are of considerable interest.

**SUMMARY.** 1. This case presents many points of interest, both from the pathologic and surgical sides, including the obstinate character of the original inflammation in the frontal sinus and the exposure of the dura in the course of one of the operations through which the infection passed to produce the extradural abscess.

2. It is unfortunate there was no bacteriologic examination made from the sinus secretion at the time of the original operation.

3. The value of nitrate of thorium as an aid in differentiating

between an extradural and a cerebral abscess during a roentgen-ray examination.

4. The complete relief of the osteomyelitis, generally a progressive condition.

5. The fulminating process developing so rapidly and resulting in a subdural abscess after the extradural abscess had seemed to be relieved.

## BENIGN DECIDUAL TUMORS OF THE UTERUS.\*

BY JOHN BENJAMIN NICHOLS, M.D.,

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THERE are a number of varieties of benign uterine polyps, some occurring in the non-pregnant uterus and some originating from the structures peculiarly associated with pregnancy. The polyps of the non-pregnant uterus are of two chief types: the mucous polyp, derived from the uterine mucosa or endometrium; the fibroid polyp, an intra-uterine fibromyoma. The gestational polyps best known are the hydatidiform, fleshy or other polyps derived from chorial structures; fibrinous polyps (or pseudopolyps), hardened masses of fibrin, perhaps mingled with placental debris, formed from blood clots retained after uterine bleeding; placental polyps, originating from adherent fragments of the placenta or fetal membranes retained after parturition. To these must be added, as shown by the observations presented in this paper, another type, the decidual polyp.

Both the fetal and the maternal elements of the placenta are capable of producing neoplasms, both malignant and benign. Of the fetal tissues the chorial structures may give rise to various benign moles and to the malignant syncytiomas and chorio-epitheliomas. The maternal portion of the after-birth, the decidua, may produce benign decidual polyps and malignant deciduomata. Tumors composed of both chorial and decidual elements conjointly are represented by the placental polyps, which are probably capable of undergoing malignant transformation.

The decidua is the structure lining the uterus during pregnancy; it originates from the uterine mucosa or endometrium, which undergoes special transformation during the period of gestation. It lies next to the muscular wall of the uterus on one side and is blended with the chorion on the other side. The decidua serotina, or placental portion of the decidua, is the thick, fleshy, deepest layer of the placenta. At the margin of the placenta the decidua serotina

\* Read before the Medical Society of the District of Columbia, May 19, 1920.



continues and merges into the decidua vera, a thin membranous lamina forming the deepest of the three layers composing the membranes of the after-birth. The decidua vera attains a thickness of 8 to 10 mm. by about the fourth month of pregnancy, but later becomes thinned to about 2 mm.

Histologically two layers are distinguished as making up the decidua, a broad, deeper, "spongy" layer and a narrower, more superficial, "compact," layer. The spongy layer is composed of distended and proliferated endometrial gland structures, with an intervening stroma similar to that of the non-pregnant endometrium. The glandular hyperplasia is sometimes so marked as to resemble adenoma in appearance. In the earlier months these glands are lined with a single layer of columnar epithelium, but later this epithelium is mostly lost. The compact layer of the decidua consists largely of the so-called "decidual cells," large, rounded or oval epithelioid or endothelioid cells, with vesicular, lightly staining nuclei; at times these cells present an appearance similar to that of the prickle cells of the epidermis, with intercellular intervals crossed by fine cytoplasmic projections. These decidual cells appear in the endometrium only during pregnancy. In spite of their marked epithelioid appearance these cells are believed to originate from connective-tissue cells. The ducts of the endometrial glands traverse the compact layer during the earlier period of pregnancy but disappear after three or four months. The epithelium lining the uterine cavity in the non-pregnant period becomes in the decidua gradually thinned out and finally disappears.

The histologic elements making up the structure of decidual polyps are those of the normal decidua itself, that is, its stroma, glandular and vascular structures and decidual cells, mingled in varying proportions. An exaggeration of the tendency to glandular proliferation in the normal decidua may result in distinct, if not distinctive, adenomatous development. The stroma and glands may not, however, present an appearance essentially different from that of ordinary polyps of the non-pregnant uterus, but the presence of the characteristic epithelioid decidual cells is distinctive and conclusively indicates the decidual character and origin of the growth. Although chorial tissues (villi, etc.) necessarily develop in intimate association with the decidua, an exclusively decidual tumor should contain no or but minimal traces of chorial structures. Growths consisting of a mixture of chorial and decidual elements belong to the somewhat different and better recognized category of placental polyps.

In judging as to the character of a growth containing decidual elements it is necessary to take into consideration certain related conditions which must be differentiated or evaluated before the growth can be regarded as a true deciduoma. These conditions

are the "decidual reaction," mucous polyps, hyperplastic decidual endometritis and placental polyps.

The process of conception and early embryonic development sets into action a stimulus that results in the transformation of the non-pregnant endometrium into the gestational decidua—the "decidual reaction." This stimulus to decidua formation is effective not only at the site of implantation of the embryo but also at more distant localities. Thus the endometrium undergoes decidual development (that is, the formation of decidual cells) even in extra-uterine gestation when it is not involved in real placenta formation. Furthermore, other structures than the uterine mucosa may exhibit decidual changes, such as the development of the characteristic decidual cells. Thus in tubal and ovarian pregnancy the tissues of the tube or ovary undergo decidual transformation. Decidual changes have also been observed postmortem in the subperitoneal connective tissue of the pelvic region, as in the floor of Douglas's pouch, the lateral pelvic walls, the surface of the ovary and uterus, the pelvic colon, the omentum and the appendix; also in adenomyomata. Ley reports having seen them in the stroma of three cases of cervical erosions, being mistaken for carcinoma. He also reports a case in which polygonal decidual cells occurred in the substance of a subperitoneal fibromyoma removed at a Cesarean section; in this case the cells were regarded as derived from the muscle cells.

From these considerations it is apparent that a previously existing uterine tumor (and especially a mucous polyp, originating from the uterine mucosa) might during pregnancy conceivably undergo decidual transformation. Consequently in the case of tumors exhibiting decidual characters first observed during pregnancy or labor it is generally difficult or impossible to determine whether they originated *de novo* from the decidua during the pregnancy or were previously existing tumors manifesting the decidual reaction. A full knowledge of the previous conditions may be necessary to settle the question, and this is obviously liable to be lacking. Further systematic study of the frequent cases of uterine tumors complicating pregnancy should throw light on this question.

Decidual endometritis is an inflammation of the decidua or endometrium of the pregnant uterus, just as ordinary endometritis is inflammation of the endometrium of the non-pregnant uterus. Among the varieties of this condition, which have been long recognized, is hyperplastic decidual endometritis, which consists of an overgrowth of the decidua. This overgrowth may be either general—"endometritis decidualis hyperplastica diffusa"—or circumscribed (usually termed "polypoid")—"endometritis decidualis hyperplastica polyposa."

It is conceivable that a general thickening of the decidua might take place in connection with death of the embryo in the first weeks

of pregnancy, and hence exhibiting little fetal or chorial structure; and that this decidua might become separated and expelled from the uterus as a fleshy mass or pseudo-tumor, with a central cavity. A possible though not certain case of this kind is on record (Maier).

Again the distinction between a localized hyperplasia of the decidua and a decidual tumor might be more or less academic.

Placental polyps are intra-uterine growths originating from fragments of placenta or membranes retained after labor. Whether their development is initiated at the time of labor or antedates that time they become clinically manifest only after parturition. The symptoms indicating their occurrence (hemorrhage, malignant change, etc.) sometimes appear a very short time after labor, sometimes only after the lapse of months or years. These growths consist of a mixture in varying proportions of chorial and decidual elements, which have undergone hyperplasia and formed tumor-like masses. They necessarily must have, or at some period must have had, a decidual foundation giving them organic connection with the uterine substance. Ordinarily placental polyps probably contain a large or considerable proportion of chorial structures, but it is conceivable that with early death of the embryo, arrest or failure of development or atrophy of the chorial structures, or for other causes, only the hyperplastic decidual portion of the growth would be left with but minimal or imperceptible traces of the chorion. Such a growth might be entitled to the appellation of a decidual tumor, and yet its origin and pathologic characteristics would be identical with those of placental polyps. Decidual tumors developing subsequent to abortion or labor therefore practically belong to the category of placental polyps; at least it would be difficult to draw an absolute line of distinction between the two.

The foregoing considerations afford criteria by which we can estimate the pathologic position of decidual tumors. The observations which I shall present demonstrate the occasional, if rare, occurrence of benign uterine tumors exhibiting predominantly decidual characters and containing no (or but minimal) traces of chorial tissue. Some of these develop during the period of gestation long before parturition; these are least doubtfully entitled to the designation of true deciduomata. It seems quite conceivable that these tumors could arise *de novo* from the decidua of the pregnant uterus, and yet we are not now in a position to exclude the possibility of their being previously existing uterine polyps that have undergone the decidual reaction. Other cases of tumors of predominantly decidual structure develop subsequent to parturition, but these practically and essentially pertain to or merge into the somewhat different and better recognized category of placental polyps.

The term *deciduoma malignum* in strictness should denote a sarcomatous tumor originating from the mesoblastic elements of the

decidua or possibly an adenocarcinoma originating from decidual glands (if identifiable as such or distinguishable from an ordinary endometrial adenocarcinoma). The frequent use of the expression deciduoma malignum as synonymous with chorio-epithelioma is obviously a misnomer, since the latter essentially involves chorionic epithelium only and not decidual elements.

I have found in the literature extraordinarily few reported cases and studies of benign deciduomata, so few as to make possible only a beginning of a casuistic and epicritic of the subject; though other observations are perhaps buried in articles on uterine tumors in general or tumors complicating pregnancy, etc., whose indexed titles are too general to afford a clue to their contents. Altogether (down to 1920) I have found only about six or seven reports of cases, covering only three or four unquestionable examples of benign decidual tumors, besides some doubtful cases. In addition to these I have had the opportunity of observing and studying two cases.

These cases can be best divided and considered in two classes: (1) Antepartum deciduomata, appearing or at least obviously developing during the period of pregnancy and prior to parturition, which are the truest type of the tumor; (2) postpartum tumors, on the order of placental polyps, which may develop after delivery or after death of the embryo from bits of retained decidua.

The details of the cases are as follows:

**I. Antepartum Deciduomata.** The first two cases are from my personal observation.

**CASE I** (from Dr. F. Yates).—Mrs. A. E., housekeeper. Previous history negative.

At the age of thirty-three years, after being married for about nine years, she became pregnant for the first time. On May 22, 1916, in about the fourth or fifth month of this pregnancy, a polyp about 1 cm. in diameter projecting from the os uteri was removed.

The substance of this tumor consisted largely of masses of large epithelioid cells—decidual cells. Mingled with them were small round cells. Thin-walled vascular channels were plentiful, and glandular elements were present, chiefly in the form of round, dilated or cystic cavities, with a thin epithelial lining. The exterior of the polyp was covered with a thin layer of low epithelium cells.

The patient aborted May 31, 1916. The placenta on gross and microscopic examination appeared normal. The mother's blood gave a negative Wassermann reaction.

The subsequent history of this patient, covering a period of four years, has been normal, and there has been no return of neoplasm.

**CASE II** (From Dr. G. S. Barnhart).—Mrs. E. J. B., housekeeper, aged thirty-nine years. Married about 1911. Had no children at term but two abortions occurred at about the third month, on December 8, 1914, and November 25, 1915. Hemoptysis, November 3, 1915.

Another pregnancy occurred in 1917, the last menstruation taking place July 20, 1917.

On October 9, 1917, a polypoid growth, about the size and shape of a Malaga grape, projecting like a finger tip from the cervix uteri, was removed in fragments; the growth was vascular and bled freely; uterus slightly enlarged.

On microscopic examination the tissue was shown to consist chiefly of masses of large epithelioid cells—decidual cells; they were rather loosely applied together, with slight intervals between them resembling those of prickle cells. Small round cells were scattered through the tissue and also aggregated in masses, especially at the periphery. No glandular structures were present. Bloodvessels and sinuses were rather plentiful and the periphery was hemorrhagic. The surface of the fragments showed little condensation of tissue to form a capsule. Superficial epithelium did not appear in the sections.

Examination of the uterus October 13, 1917, showed that the growth had entirely disappeared.

Quickening occurred December 5, 1918. There was no recurrence of polypoid outgrowth. On April 29, 1918, at full term occurred normal delivery of a female infant weighing seven and one-eighth pounds. The membranes showed a few gray, thickish, subchorial plaques, which microscopically were seen to be formed of aggregations of decidual cells. Similar subchorial gray plaques occurred also on the placental surface.

The puerperium was normal, the mother and child doing well. The patient has since been normal (two and a half years) and there has been no recurrence of uterine neoplasm. She has recently passed through another pregnancy, with normal delivery at full term, on May 18, 1920; placenta normal.

A case corresponding to the foregoing two cases was reported by Stolper, of Vienna, in 1902, as follows:

CASE III.—A woman who had had four previous pregnancies (two of which had ended in abortion, the last abortion three years previously) consulted Stolper September 5, 1901. The last previous menstruation had been on July 19, 1901. She complained of a sensation of upward pressure, anorexia, pains in left chest and weakness. General examination was negative. Uterus retroplaced, large and soft; cervix hard, eroded. From the os protruded a polyp, about the size of a bean, its surface appearing like mucous membrane, and bleeding at the least disturbance; it was attached by a pedicle extending up above the internal os beyond the reach of the examining finger. A small piece of the growth was removed for microscopic examination, which disclosed its decidual structure and the existence of pregnancy. A few days later the patient returned, complaining of an increase of pressure and pains. He

removed the polyp, after which hemorrhage quickly ceased and the sense of pressure disappeared. Seven or eight weeks later, on October 29 (fourth month), the patient aborted, discharging a fresh fetus 14 cm. long. The placenta showed no abnormality and the membranes were complete.

The tumor, 2 cm. long and 0.5 cm. in diameter, had a lobed surface covered with necrotic tissue, blood and fibrin; in places were remains of an epithelial covering in the form of small thin protoplasmic layers with scattered nuclei but undivided into distinct cells. The substance of the tumor showed a distinct differentiation of spongy and compact portions. The superficial compact portion consisted mainly of large decidual cells, with some smaller cells interspersed, and with large vascular channels. The center of the tumor was made up of a mass of parallel gland tubes running lengthwise in the tumor, with scanty intervening small cellular elements; the epithelial lining of the gland tubes was composed of cubical cells, in many places degenerated, in other places completely lacking.

Stolper discusses whether this tumor originated from the decidua vera or was a preëxisting mucous polyp that underwent decidual transformation when the pregnancy set in and upholds the latter view of the origin of the tumor. This point will be considered later.

A case of a decidual adenoma, of quite different character from the three foregoing cases, was reported by Hitschmann (of Vienna?) in 1900.

CASE IV.—A woman, aged thirty-six years, who had had a normal pregnancy in 1892, in her second pregnancy last menstruated July 24, 1897, and was delivered April 24, 1898. After delivery of the placenta bleeding continued; on introduction of the hand into the uterus a tumor surrounded by blood clots was found detached and loose in the uterine cavity. This tumor was 8 by 4 by 2.5 cm. in size and consisted mainly of a spongy or honeycomb-like mass of proliferated glandular cavities, ranging up to pea-size. The superficial portion of the tumor, covering the glandular masses, consisted of a thin layer (not over 1 mm. thick), made up largely of decidual cells and corresponding to the compact layer of a decidua. The gland cavities were lined with glandular epithelium, partly well preserved, partly partially degenerated. No chorial elements were present. The placenta and membranes showed no abnormality.

This tumor was essentially an adenoma, originating from the proliferated glandular elements of the spongy portion of the decidua and becoming detached during labor.

Hitschmann considers the possibility of this tumor having been in existence as a mucous polyp prior to the beginning of the pregnancy and undergoing decidual transformation along with the rest of the endometrium during gestation. He concludes that the tumor probably originated during the gestation.

A case of a uterine fibroid containing isolated masses of decidual

elements was reported by Melnikoff-Razvedenkoff, of Russia, in 1907, as follows:

CASE V.—A woman, aged thirty-five years, married for nine years, suffered painful and profuse menstruation, and about May, 1901, had metrorrhagia for eight weeks. A few months later she became pregnant, the last menstruation occurring September 10, 1901. She developed nephritis and dysuria, and was found to have two fibroid tumors in the uterine muscular substance, toward the peritoneal surface. Hysterectomy was performed by Michin February 6, 1902 (fifth month), with recovery from the nephritis. Five years later the patient was in good health and had developed no malignant conditions.

One of the tumors was a simple myoma, of the size of a goose egg. The other tumor, fist-sized, was of fibromyomatous substance in which were imbedded foci of decidual tissue (spongy), with decidual cells and gland structures, each focus with a little cleft-like cavity; there was also a small isolated canal-like cavity lined with cuboidal epithelium, with internal papillæ and surrounded by a muscular sheath. These foci and the canal were unconnected with one another or with the interior of the uterus, and were regarded as isolated rudimentary supernumerary uterine cavities imbedded in a fibromyoma and undergoing gestational changes simultaneously with those of the pregnant uterus. The tumor was benign.

The earliest report of cases of decidual tumors which I have found is an account of two alleged cases by Maier, of Freiburg, published in 1876. Although this author asserted that these tumors were of decidual nature his descriptions and illustrations of their histologic characters do not agree very well with those of the typical decidua; there is therefore some obscurity and doubt about the true nature of these cases. Maier's two cases were as follows:

CASE VI.—A woman in her third pregnancy, at the twenty-second to twenty-fourth week, gave birth to a fetus, with a placenta and a tumor, the tumor being delivered first, the fetus and placenta half an hour later. The tumor was 9 by 7 by 3 cm. in size, lobed and lobulated. Histologically it exhibited a reticulated or mesh-work structure, the network composed of spindle-shaped cells, the cavities occupied by large cells stated to be decidual cells; both kinds of cells were regarded as being of substantially identical character, merging into one another. The cells were in contact with one another, without intercellular elements.

According to Sängner (1891) this patient died later of carcinoma uteri.

This tumor may have been, and probably was, a decidual polyp, detached at the time of labor, but the histologic description (especially in view of the later malignancy) is not convincing as to its decidual character.

CASE VII.—A woman in the forties, mother of several children, previously healthy. In the previous year she had suffered frequent bleeding during and between the menstrual periods. Examination showed the presence of a tumor protruding from the os uteri, which was removed. The tumor was  $3\frac{1}{2}$  to 4 cm. long,  $2\frac{1}{2}$  cm. in diameter; cylindrical in form and hollow, having a longitudinal central canal; the anterior wall 2 cm. thick, the posterior 2 to 4 mm. thick. The tumor had a finely porous or alveolar structure, and on squeezing small plugs of smeary material were forced out of the cavities. The framework was partly made up of connective tissue, and the cavities were occupied by large spindle and other cells regarded as decidual cells. There were small cellular tufts ("decidual" not chorial) projecting into some of the alveolar spaces.

The tumor appeared to be a cast of the uterus, formed of a thickened mucosa or decidua, which became loosened and was cast off. Its decidual character does not seem to be demonstrated by the histologic description; if decidual, it might be classed as a case of endometritis decidualis hyperplastica diffusa.

II. *Postpartum Deciduomata*. A case verging on the category of placental polyps reported by Klotz, of Innsbruck, in 1886-87, was as follows:

CASE VIII.—A woman, married at the age of twenty-four years, within a period of seven years had four full-term births and three miscarriages, all of normal character except that the placenta had to be removed after a premature birth in the seventh month. The last of these labors was a normal delivery at full term, the after-birth coming away completely and spontaneously. Two months after this confinement she consulted Klotz for a uterine discharge, and a careful uterine examination at this time revealed nothing abnormal except the discharge. For two years after this she menstruated regularly and normally and enjoyed complete good health. Then (at the age of thirty-three years) she had profuse uterine hemorrhages for a period of five weeks, which finally almost exsanguinated her. Examination revealed an enlarged uterus, containing an oval goose-egg sized bleeding tumor attached by a broad pedicle to the posterior uterine wall and projecting into the dilated cervical canal. Removal of the tumor resulted in a cure of the hemorrhage, and a year later she had another normal pregnancy and labor.

This tumor was of "longish, roundish" shape; dark brown-red; soft consistency; on slight pressure thick pulpy blood exuded from cut sections. It possessed a somewhat spongy structure and was composed largely of masses of large rounded cells in close apposition—indistinguishable from decidual cells. Smaller proliferating cells and round cells were also present. Numerous branching gland structures were present, lined with distinct epithelium. Large vascular sinuses, lined with endothelium and filled with blood and cellular debris, were also present, apparently interposed between the terminal arterioles and venules. The surface of the tumor was



lined with a single layer of epithelium, in places columnar, in other places flat or even a continuous layer of protoplasm (syncytial), with nuclei at regular intervals. No chorial tissue or fetal structures were present. The structure suggested that of an early decidua serotina.

As at the previous parturition the placenta had been discharged complete and an examination two months later disclosed no morphologic abnormality of the uterus, this tumor could hardly have been derived from a retained portion of secundines from a previous pregnancy. The only explanation for it available was that it resulted from an abortive pregnancy of very brief duration, in which the gestational stimulation was sufficient to cause the development of a decidua serotina, but on account of [early] death of the impregnated ovum not producing any fetal placental elements.

The growth might therefore be classed as an abortive placenta, with proliferation of the decidual tissue.

The following case was reported as a deciduoma by Küstner, of Jena, in 1881:

CASE IX.—A woman who between her twenty-first and fortieth years had had eight normal full-term labors, at the age of forty-two had an abortion, about eleven weeks after her last menstruation, discharging a fetal and placental mass of the size of a goose egg. This was followed by continued bleeding, necessitating operation a month later. Examination of the uterus then showed the presence of two flat bean-sized projecting masses (the thicker about 1 cm. in breadth) attached to the wall of the uterine cavity. The tumors were removed, resulting in cessation of the bleeding and recovery. Microscopic examination showed the growths to consist of a stroma of large spindle and rounded cells, in which were imbedded numerous gland tubes lined with long columnar epithelium. No superficial epithelium was found. In places, mixed with blood clots, were sparing but indubitable chorial villi. The decidual compact layer and large cells were little or not at all in evidence; but the presence of chorial villi established the gestational origin of the tumors in this case.

In 1883 Küstner reported eight additional similar cases of tumors regarded (although lacking chorial elements) as of decidual character and following known or assumed abortions. In the absence of decidual cells or chorial structures the decidual character of these cases of Küstner is not completely demonstrated, as differentiated from non-gestational endometrial growths; certainly if deciduomatous they must have originated at an extremely early period of gestation prior to the time of development of distinctive decidual structures.

Numerous cases of placental polyps are on record which it is unnecessary to cite in this connection.

From the foregoing collection of case reports may be gathered four clear cases of benign antepartal decidual tumors—one case of

an intra-uterine decidual adenoma appearing at a full-term labor (Case IV) and three cases of decidual polyps found protruding from the external os uteri in the third to fifth months of pregnancy (Cases I, II and III). Of the last three cases two aborted and one went to full term. The benign character of the growths in Cases I and II is attested by the normal subsequent histories of the women for two to four years.

The rather academic question whether these tumors developed from the decidua *de novo* during pregnancy or were polyps previously existing that underwent decidual transformation under the special conditions of gestation cannot be finally decided from the evidence available. There is nothing intrinsically improbable in the idea that a tumor could develop directly and primarily from decidual tissue, especially as the latter is such an actively growing structure. The character of the epithelial covering of the polyps may have some bearing on the question. In Case II the absence of surface epithelium would suggest that the polyp was a recent rapid outgrowth of the decidua, and therefore, like it, lacking an epithelial covering. In Case III the primitive and imperfect character of the surface epithelium would similarly suggest recent decidual origin. In Case I the more perfect and uniform character of the epithelial covering might better suggest the possibility that this was a pre-existing polyp that with the onset of pregnancy assumed decidual characters. My own impression is that these tumors can arise *de novo* from the decidua.

**Summary.** Tumors exhibiting decidual characteristics may develop during the period of gestation, appearing either as polyps protruding from the os or as intra-uterine tumors found at the time of parturition. Although their microscopic appearance somewhat resembles epithelioma (or endothelioma) they are strictly benign and should not lead to needless radical operation. Whether they originate from the decidua *de novo* or are previously existing tumors that have undergone decidual transformation cannot be finally stated; the former seems probable. The identification of the decidual character of such polyps is an indication of the existence of pregnancy.

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## THE HUMAN PRE-HALLUX.

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THE presence of supernumerary bones in human feet has for some years been recognized by the medical profession. The frequency with which these bones occur, however, their probable origin, and, above all, the pathologic significance of their presence, are phases of the subject that have received little attention.

It is probable that all of the supernumerary bones of the feet, although occurring in such diverse anatomic positions, are attributable to the same general cause and bear the same relation to disease. In determining what this general cause may be, a detailed study of one of the supernumerary structures is of more value than a broad survey of the whole group. For this reason no attempt has been made in the present article to deal with the many supernumerary bones appearing in human feet, bones whose positions and shapes are already well known. Rather, one structure alone has been taken up with a view of determining both its cause and its significance. This structure I have termed the "human pre-hallux," a term more truly descriptive than any by which the structure has been previously designated, since in both position and form it appears to be directly homologous with the pre-hallux observed in many of the so-called "lower" animals.

The pre-hallux is the largest of the supernumerary structures appearing in human feet, and probably the most troublesome. It is far more common than is ordinarily supposed. While it is impossible to estimate the frequency of its occurrence in the sum total of feet, it is to be found in about one case in ten of the painful feet that have come under my observation. Extensive study of feet in the roentgen ray has shown it to be the real cause of many cases of foot-trouble erroneously diagnosed as "flat-foot," "broken arches" and so forth. In fact, many other forms of foot trouble, such as "rheumatism," "gout" and similar ailments, are often shown by the roentgen ray to be but the accompanying conditions of this erratic bone development.

Growing from the inner border of the scaphoid (Fig. 1), and directed downward and somewhat backward, the pre-hallux is in a position to receive much of the weight of the body, and is, accordingly, a constant point of pressure and of pain. The surrounding tissues become irritated and swollen and the owner of the foot becomes a sufferer from "gout," "rheumatism," "flat-foot" or "broken arches," according to his fancy and the reading matter that has chanced to come his way. If he seeks professional aid the treatment offered him will depend entirely upon the source of his

counsel. He may be given an arch. He may be put on a diet. He may be instructed in foot-exercises. He may be admonished to keep off his feet. He may be advised to have a "redressing." Or he may be given what he in all probability needs, a Wassermann and antispecific or tuberculin treatment, and in some cases surgical aid.

**Significance of the Pre-hallux.** The pre-hallux in human feet has two possible interpretations: (1) It may be regarded as an evidence of diseased and degenerate feet whose degeneracy allows old and once-atrophied structures to redevelop; or (2) it may be looked upon as Nature's normal and healthy effort to brace a rapidly abducting member and adjust it to its ever-increasing responsibility. Thus it is an open question whether the human pre-hallux is a reversion to a lower ancestral form or whether it represents a further stage in evolution and foreshadows a future, normally six-toed human foot.

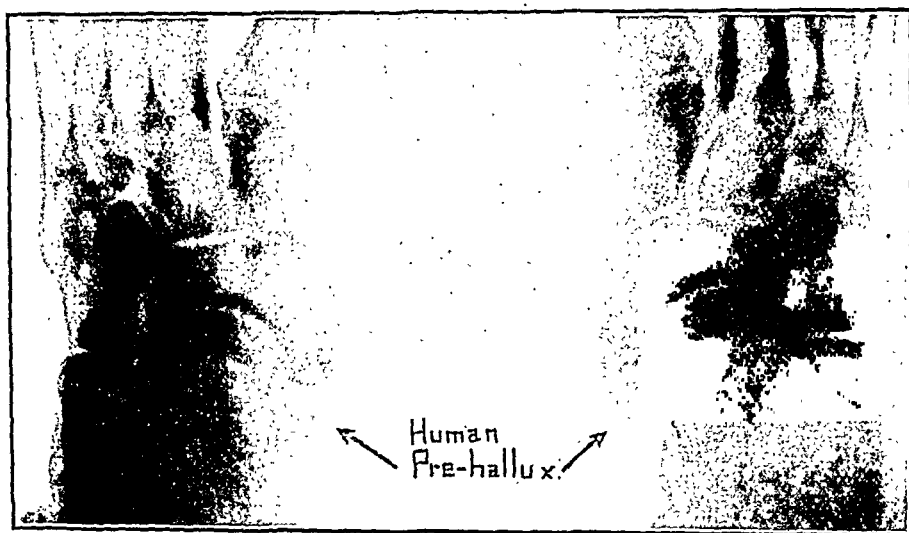


FIG. 1.—Showing articulation of human pre-hallux with scaphoid.

If the first interpretation is correct the pre-hallux should appear only in association with some degenerating disease, a history of which, by sufficient thoroughness of investigation could be obtained. If the second is correct the pre-hallux-bearing foot should be a healthy, normal member, the advance agent of a more efficient human foot-type.

Again, if the first hypothesis is correct we should be able to find traces of the old "ancestral form" among the direct ancestors of the human foot, and, according to the teachings of convergent evolution, they may appear among the members of other orders and other groups as well. That these traces exist in ample measure is shown by the animal series that follows. If the second hypothesis is correct the pre-hallux, as Nature's adjustment of individual form

to function, should appear only when a similar function makes necessary a similar adjustment. Since man is the only animal who has so far perverted his feet as to make them inadequate to the duties imposed upon them, we should, in this latter case, expect to see the pre-hallux only in human feet.

My observations of pathologic conditions coexistent with the pre-hallux, as well as my original researches among the foot-structures of lower vertebrates, lead me to incline toward the former theory, namely, that the human pre-hallux signifies reversion to a lower form, brought about probably by constitutional disease.



FIG. 2.—Left hind foot of *Rana montezuma*.

**The Pre-hallux in Lower Vertebrates.** The pre-hallux, while not a congenital structure in human feet, exists normally and is congenital in the feet of many of the lower animals. There are few orders in which it does not somewhere make its appearance. Even in those orders in which it is most frequently seen, however, the pre-hallux is extremely inconstant and gives no regular history of either evolution or devolution. It appears among the amphibia, the reptilia and

the mammalia with apparent disregard of both family history and individual need, developing in some forms into a well-marked toe, remaining in others a mere nodule of bone fused with the scaphoid. It is seen in some very primitive forms; it is well-marked in some animals that are in many respects the most specialized of their kinds.

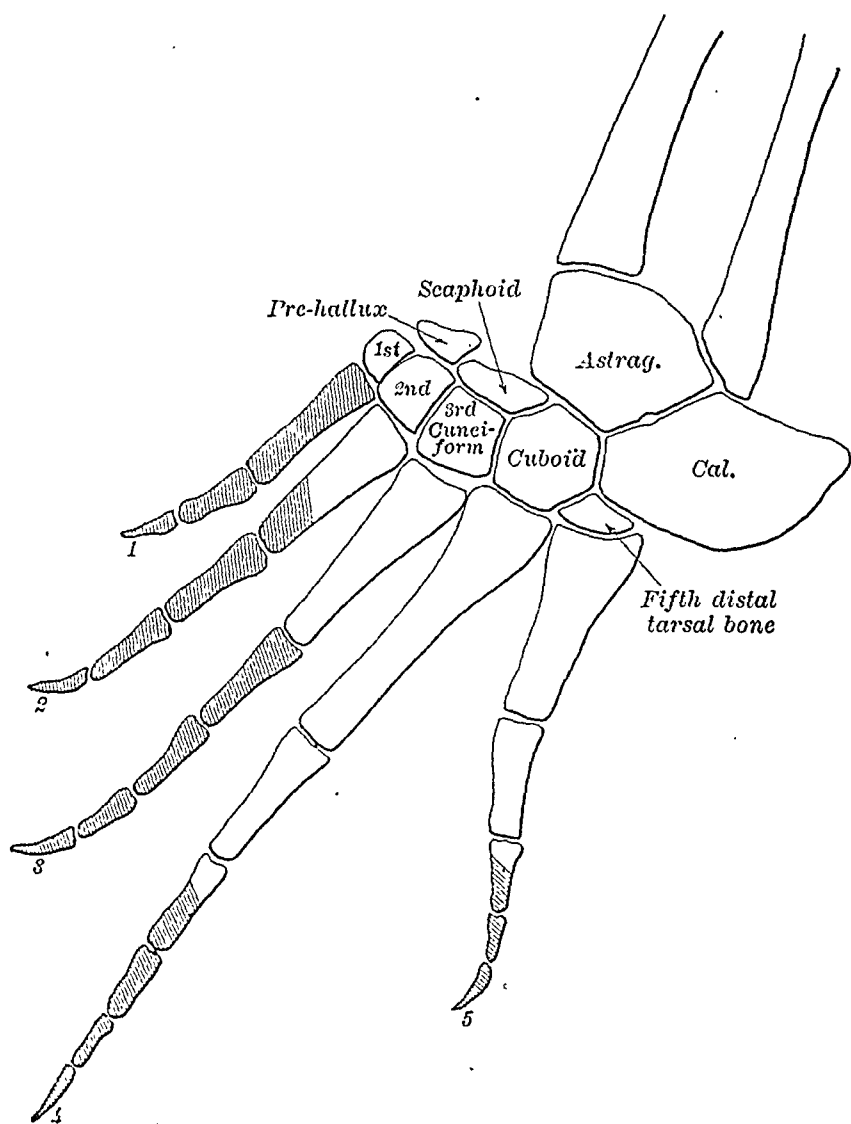


FIG. 3.—*Broomia perplexia*. (After Watson.)

It appears in foot-structures where it has no apparent value and fails to appear in others that would seem to most demand its presence. In short the pre-hallux even in lower vertebrate feet gives every evidence of being the remnant of some ancestral form of the past.

Just what this ancestral form may have been has yet to be discovered. Because of the lack of known links between the fins of the

fishes and the feet of the amphibians it is impossible to picture the exact stages by which the old fin-rays were fused or atrophied into the elements of the early amphibian foot. That the land-vertebrate foot, however, is but the adaptation of a fin-like appendage for weight-bearing and terrestrial locomotion has long been a generally accepted fact. The fin, therefore, being assumed the ancestor of all vertebrate feet, may be taken as the original source of all the ossification centers in such feet, and the atrophied fin-rays may be regarded as the source not only of the pre-hallux but of all the other supernumerary bones of the foot as well.



FIG. 4.—Right hind foot of echidna.

In some of the oldest known foot-structures we see a retention of the ancient elements in the pre-hallux and the fifth distal tarsal element. The *eryops* shows both of these elements. The *eryops*, although a member of the amphibia, was apparently but partially adapted to land-life and resembled in some ways some of the very ancient fishes. It is the nearest approach to a link between the fishes and the amphibians yet found.

Higher up among the amphibia we see the pre-hallux conspicu-

ously displayed in the foot of the frog (Fig. 2). The supernumerary structure is well-developed and in some species, particularly in *Rana montezuma*, shows two distinct segments. Thus we find the pre-hallux in both the most primitive and the most highly specialized members of this group, seeming testimony that the old ossification centers may be long-atrophied but never lost and may be indefinitely the seeds of new-bone developments.

Among the reptilia the foot of the lizard *Broomia perplexia* (Fig. 3) illustrates a possible type of transition between the pre-hallux of the eryops and that of later forms. A diminishing of the fifth distal tarsal element is also seen as the fifth metatarsal swings around toward the cuboid. As a matter of interest let me say that

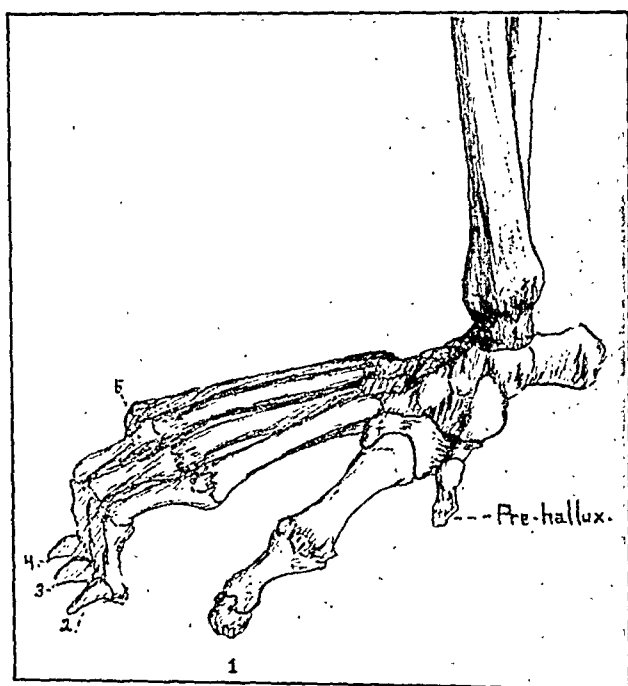


FIG. 5.—Right hind foot of opossum (*Didelphys*).

this fifth distal element, as well as the pre-hallux, appears normally in the feet of various animals notably some of the apes, and frequently appears as a supernumerary bone in human feet.

The pre-hallux is first seen in the mammalian group in the foot of the echidna (Fig. 4), one of the two representatives of the lowest of the mammalian orders, the monotremata. The hind foot is directed backward as in some reptiles and still retains the position a fin or paddle might assume if flexed for weight-bearing and terrestrial locomotion.

In the opossum (Fig. 5) a member of the order marsupialia, the pre-hallux, is pronounced and shows variation, without apparent reason, in the number of segments it possesses. In one form it shows



two distinct segments, in another only one. In the first case the pre-hallux articulates with the internal cuneiform and in the second with the scaphoid.

In the order insectivora the pre-hallux is well-marked in the foot of the Madagascar hedgehog (Fig. 6).

The pre-hallux, even among the lower vertebrates, is not always so well-marked as it appears in the case of the opossum and the

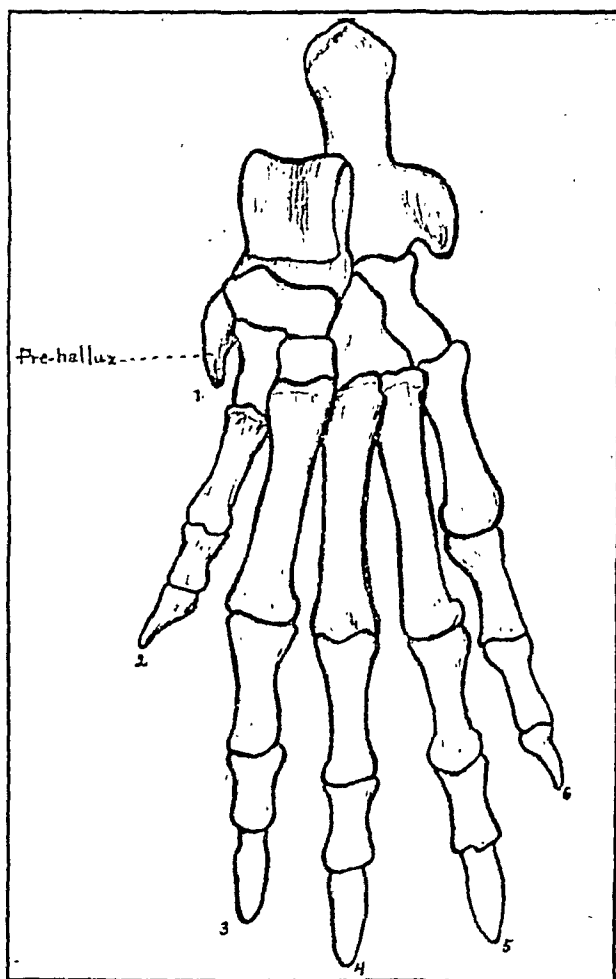


FIG. 6.—Hind foot of Madagascar hedgehog.

Madagascar hedgehog, and to other observers undertaking research along this same line a word of suggestion may not be here amiss. I have found that an already dissected foot is seldom worth anything and a mounted specimen is worth only as much as the opinion of the man who mounted it. These bones are often so inconspicuous, especially in the feet of the primates, and are so little recognized by the majority of workers, that they are simply cleaned off with

the integument and fascia and discarded as valueless. Only by dissecting the foot yourself can you find out what is really there.

Among the carnivora the pre-hallux is represented in the foot of the kinkajou (Fig. 7). In this case the pre-hallux, less well-marked than in the opossum but still of considerable size, articulates with the first metatarsal and internal cuneiform, having a ligamentous attachment with the scaphoid.

Among the primates the pre-hallux is frequently found fused with the inner border of the scaphoid. Fig. 8 shows the left foot of *Cebus hypoleucus*, in which the pre-hallux is in actual process of

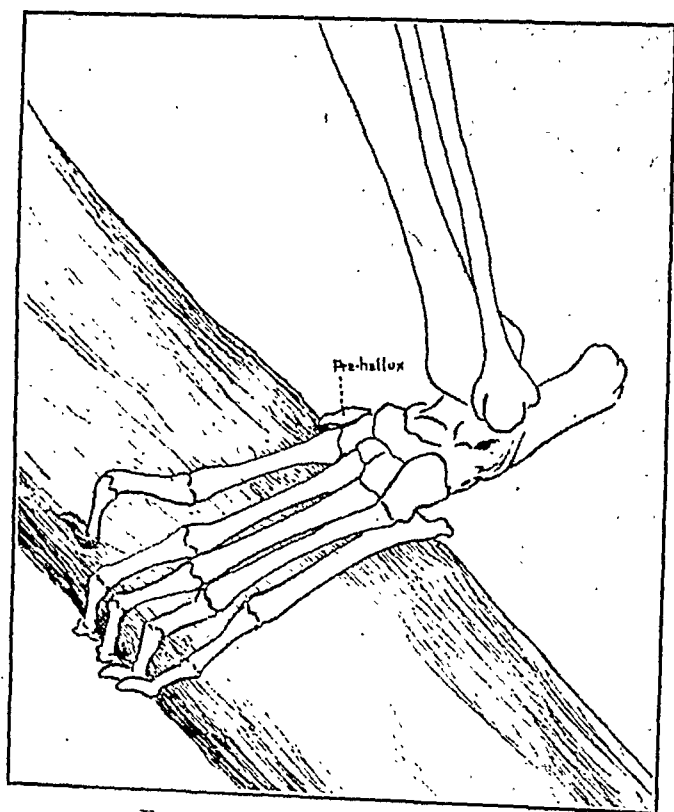


FIG. 7.—Left hind foot of kinkajou.

fusing with the scaphoid. In the right foot of the same animal the pre-hallux was still free. In both feet the suture between the pre-hallux and the scaphoid was plainly discernible.

The foot of the adult gorilla (Fig. 9) exhibits no independent pre-hallux but shows a scaphoid whose tubercle is of such size that it might well be the product of an independent ossification center.

Investigation proves that such is indeed the case. In the foot of a very young gorilla (Fig. 10), in which much of the osseous tissue of the foot is still cartilaginous, the scaphoid is seen to be the product of two ossification centers, probably the old pre-hallux and the scaphoid proper, united just above the inner border of the internal

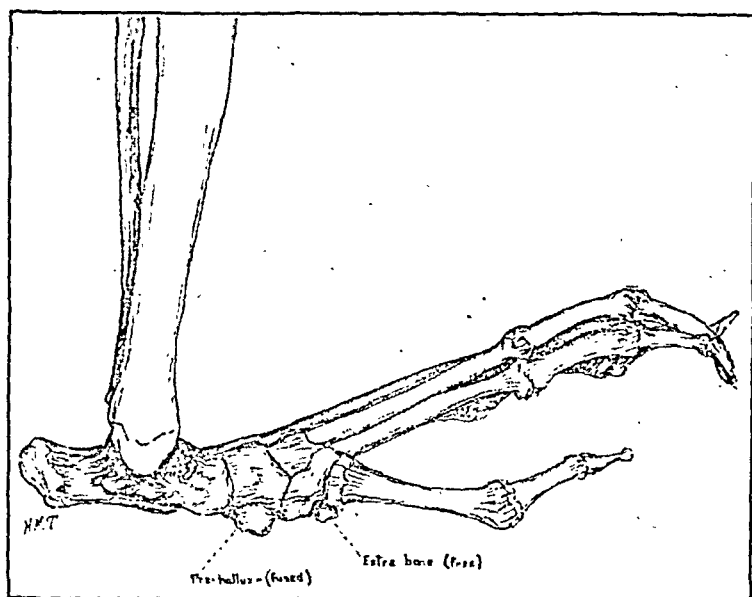
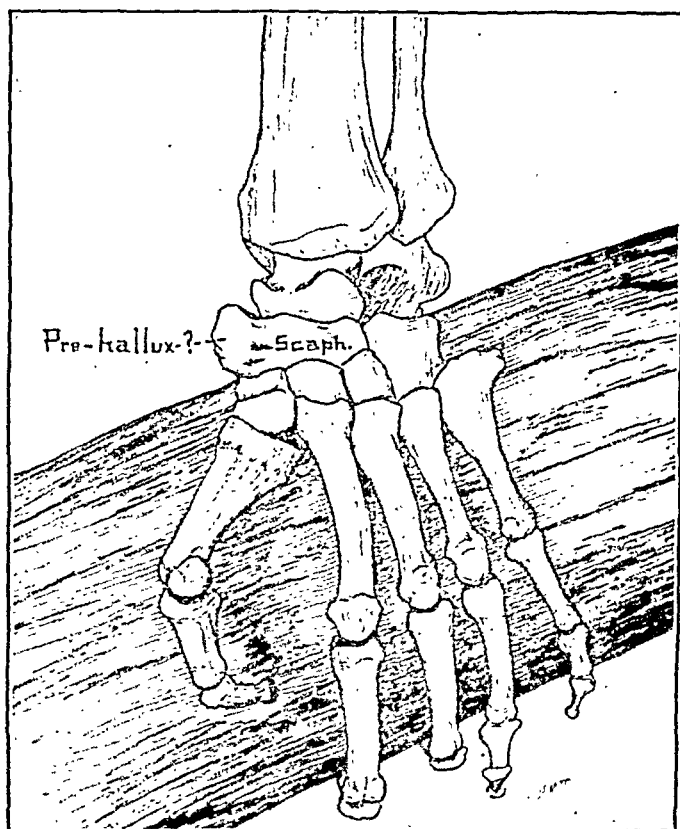
FIG. 8.—Foot of *Cebus hypoleucus*.

FIG. 9.—Foot of adult gorilla.

cuneiform. Thus the enlarged tubercle of the scaphoid in the adult gorilla is in reality homologous with the pre-hallux of various other forms.

Since such is the case, it seems beyond doubt that the greatly enlarged tubercle of the scaphoid in many painful human feet (Fig. 11) is also homologous with the old pre-hallux. This conclusion is further borne out by the observation of cases in which one foot shows the pre-hallux still free while the other foot shows a scaphoid much enlarged by the very apparent fusion of the pre-hallux. (Fig. 12).

The foot-structures of the lower animals given above do not in any way represent the entire list of lower vertebrates in whose feet

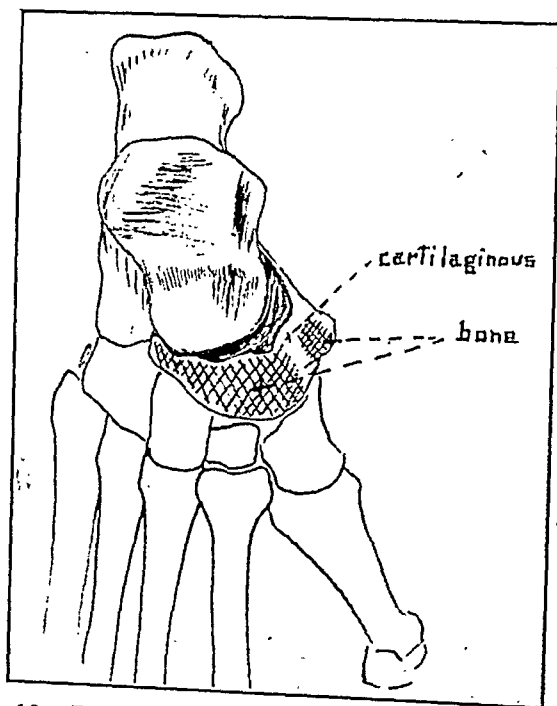


FIG. 10.—Points of ossification in scaphoid of young gorilla.

the pre-hallux is normally found. Because of the necessity for brevity I have given here only enough of the animal series to establish my point, namely, that the pre-hallux occurs normally in the feet of many of the lower vertebrates, and, in human feet, may be looked upon as a reversion.

**Relation of the Human Pre-hallux to Disease.** In admitting the human pre-hallux a reversion we immediately find ourselves facing another problem—the cause for this reversion. Popularly, all the supernumerary bones occurring in human feet are looked upon as accidental structures. We feel safe in asserting that Nature does not produce the same “accidental” structure again and again in the same anatomic position. When such a structure repeatedly appears

it is time to forget its "accidental" character and recognize it as the fixed and foreordered result of some fixed cause.



FIG. 11



FIG. 12.—Human pre-hallux fused in left foot, free in right foot.

In the case of the human pre-hallux the cause seems to be undoubtedly associated with constitutional disease. The cases under my observation give almost invariably a history of such

diseases. I have observed and photographed the pre-hallux in feet brought to operation for Charcot's disease (Fig. 13). I have

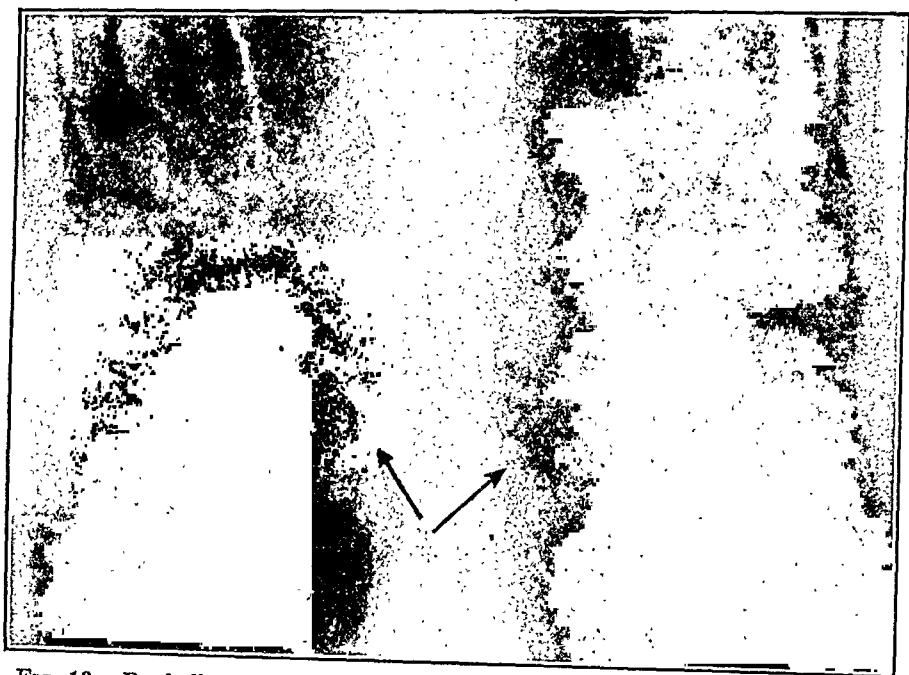


FIG. 13.—Pre-hallux in association with Charcot's disease of the proximal head of the first metatarsal.

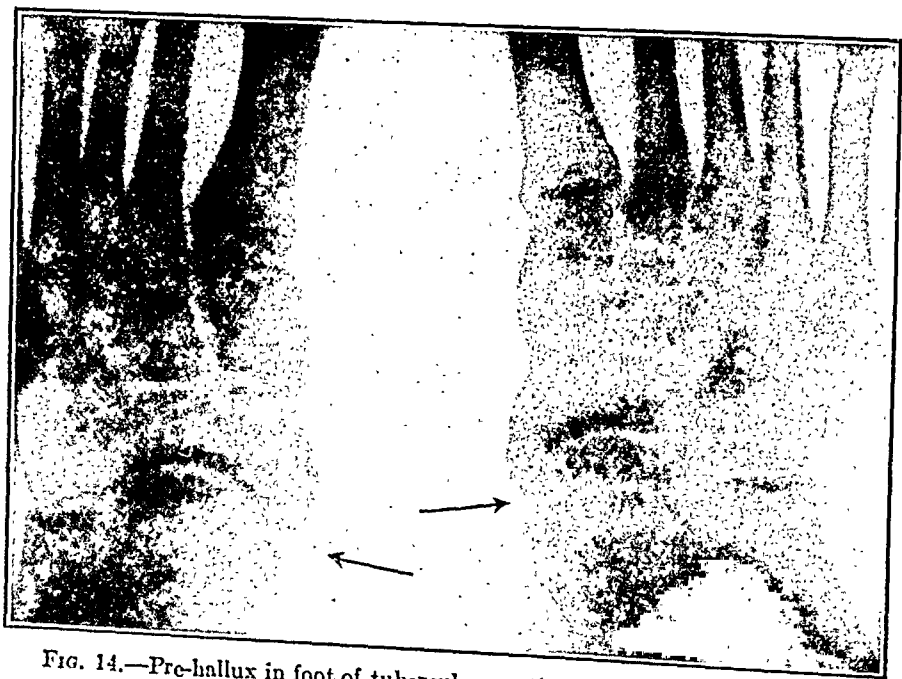


FIG. 14.—Pre-hallux in foot of tuberculous patient, a boy, aged fourteen years.

found it associated with tuberculosis (Fig. 14). I have noted its presence in feet rendered extremely painful by so-called "gonor-

rheal" spurs. While the exact cause of these spurs is still a matter of controversy, their relationship to syphilis or gonorrhea seems very probable and the presence of the pre-hallux in these same diseased feet seems of special significance.

I might go to considerable length exhibiting roentgen rays of pre-hallux-bearing feet together with the histories of the cases, but there is little to be gained therefrom. With but few exceptions—cases in most part in which I was unable to procure a satisfactory history—the pre-hallux is proved but an added affliction to an organization already overburdened with disease.

**Conclusion.** From its position, its time of development and its association with disease, therefore, I look upon the human pre-hallux as an evidence of foot-degeneration, a reversion to a lower form of foot-structure brought about by the devoluting influences of the constitutional diseases with which it is associated.

**Summary.** The human pre-hallux is that supernumerary structure growing from the inner border of the scaphoid and directed downward and somewhat backward.

It is far more common than is generally recognized, occurring in about one case of painful feet in ten.

It is the real cause of many cases of foot-trouble erroneously diagnosed as "rheumatism," "gout," "flat-foot" and "broken arches."

It is directly homologous with the pre-hallux as seen in many of the lower animals and had its ancient origin, doubtless, in some ancestral form of the past that was common to all succeeding types. Its immediate origin may be considered the dormant ossification centers left in all feet by the atrophied fin-rays.

It is not a congenital structure in human feet but appears usually between the ages of twenty and forty in association with some constitutional disease, notably syphilis or tuberculosis.

From the foregoing facts the human pre-hallux may well be looked upon as an evidence of foot-degeneration—a reversion to a lower form of foot-structure.

I wish to express my appreciation to Dr. Wm. K. Gregory, of the American Museum of Natural History, for placing at my disposal many unmounted specimens.

THE GRAVITY RESISTING ABILITY OF THE CIRCULATION;  
ITS MEASUREMENT AND SIGNIFICANCE  
(BLOOD PTOSIS).

BY C. WARD CRAMPTON, M.D.,

BATTLE CREEK, MICHIGAN.

THE estimation of the ability of the circulatory apparatus is of considerable importance, both to the physiologist and to the clinician. The heart has been studied extensively and with great care, but the balance of the circulation has not been investigated to the same degree, although modern physiology has recognized the fact that the condition of the circulatory apparatus other than the heart is of paramount importance in the variations of the blood-pressure and the distribution of the blood.

The simplest way to test the circulation is to give it a standardized amount of work to do and to note its reaction to this work, estimating what is normal and what is abnormal by the character or extent of the reaction. Exercises of various kinds have been used, such as hopping a certain distance or lifting weights of a prescribed number of pounds a standard distance at a standard rate, observing the increase in heart-rate and blood-pressure and their return to normal. The Kahn and Barringer tests are examples.

The writer has suggested<sup>1</sup> the use of a standardized load which may be imposed upon the circulation simply and easily and in an entirely natural manner. This consists in observing the reaction of the circulation to the hydrostatic load placed upon it when the subject rises from the horizontal to the vertical position. When the subject is lying horizontal the heart pumps blood, roughly speaking, in about the same horizontal plane and the blood returns to the heart still in this plane without having to be propelled or drawn upward to the heart. On rising to the standing position, however, the blood must return to the heart from the lower body against the attraction of gravity. It must be propelled or pushed from below or drawn from above, upward to the heart level. The mechanism for the accomplishing of this purpose consists in the contraction of the muscles of the legs upon the veins of the legs; the muscles of the abdomen contracting upon the abdominal contents and increasing the abdominal tension; the muscles of the veins themselves, particularly the splanchnic veins of the abdomen, keeping the blood from collecting therein; artificial mechanical contraction of the abdomen, such as may be obtained from belts or corsets; and the aspiration of the thorax increasing as the thorax

<sup>1</sup> Crampton: A Test of Condition, Med. News, September 16, 1905. Blood Ptoxis, a Test of Vasomotor Efficiency, New York Med. Jour., November 8, 1913.



is enlarged by breathing or by exercise and decreasing when the thorax is allowed to relax and become smaller. This mechanism is complex and physiologists are not in accord as to the relative significance which should be attached to the tone of the splanchnic veins and the various other factors. The writer is inclined, after consultation with Professors Carl J. Wiggers, Frederick S. Lee and D. R. Hooker, to await the dissection of this phenomenon by the physiologists and for the present to consider the discharge of the series of functions which cause the blood to be returned to the heart in the vertical position as the *gravity resisting ability of the circulation*.

It has been found that this function varied strikingly with the general efficiency of the individual. It is best when the subject is at his best and poor when the subject is tired. It is usually high in good health and low in illness. It records roughly, at least (or possibly with accuracy), the variations of illness and gives promise of showing *how ill a patient is* regardless of the nature of the disease from which he suffers. It is not necessarily a symptom of disease, for it may be abruptly raised and abruptly lowered in a sensitive person by even such a common thing as a cigarette. It varies with the hour of the day and the temperature of the room, the condition of the mind, the state of the digestion and the like. It will vary like the pulse-rate slowly or rapidly, depending upon the external and internal conditions. Since these variations are many and large the writer cannot hope to present a full statement of their significance or the various values of the method of measurement. A few reports of the investigations conducted by other observers who have used this method and some selected observations by the author are, however, significant and will be given.

**The Rationale of the Test.** The test of the gravity resisting function of the circulation is an estimate of the efficiency of the influences which bring the blood to the heart in the upright position. These are measured in part by the rise of the systolic pressure on standing. The systolic pressure is taken rather than the diastolic, because it consists of both the diastolic pressure and the pulse-pressure: the first, an approximate measure of the tension of the arterial lake and its contents; the second, an approximate measure of the charge of blood thrown into it by the heart at each beat.

To measure the efficiency of the gravity resisting function of the circulation it would appear to be merely necessary to observe the increase in the systolic pressure or its decrease and judge accordingly.

It is true that this in itself apparently is a rough measure and may be interpreted as such. It is important, however, to recognize the fact that an increase in heart-rate *alone* will increase the systolic pressure. Therefore a rise in the systolic pressure on standing may be due in whole or in part to the increase in heart-rate. This increase in heart-rate is not an evidence of the efficiency of the gravity resisting function of the circulation, but quite to the contrary, is an

evidence of a diminution of the amount of blood given to the heart in each beat because the heart can rid itself more rapidly of the small charge than a large one. Increase in heart-rate is further evidence of an increased expenditure of effort on the part of the heart and a decrease of its nutritional efficiency on account of its decreased diastole. We have therefore come to the conclusion that the greater the increase in heart-rate on standing the less the gravity resisting efficiency.

There are therefore two elements to be taken into consideration: the increase in systolic pressure, which connotes efficiency, and the increase in heart-rate, which connotes deficiency.

The observer who wishes to get a clear picture of the circulation should note both the action of the systolic pressure and the heart-rate.

It is difficult, however, to compare two or more ratings in the same or different individuals because of the necessity of balancing the importance of these two factors. For the purpose of record, comparison and statistical handling the writer has devised a scale which balances these two influences and reads a numerical index, giving one value to consider instead of two. In constructing this scale the records of several hundred cases of normal young men were taken, and it was found that the total range of the observations (disregarding the extremes) was from plus 10 to minus 10 mm. Hg of the systolic pressure and from 0 to 44 measuring the increase in heart-rate. Finding these ranges statistically equal they were assigned equal values and each divided into fifty steps, with the fair assumption that these steps were equal in significance. This developed the original scale, which was published on the basis of normal material. Subsequently, however, records from very sick people demonstrated the necessity of extending the scale, both upward and downward, and this was done, using the same measures that had been standardized for normal material. This scale presents a useful and convenient method of stating approximately the value of the efficiency of the gravity resisting ability of the circulation.

In an earlier report the writer suggested the term "blood ptosis" and the term has since been used by Sewall.<sup>2</sup> This term may properly be applied to the condition of the circulation occurring when the gravity resisting ability of the circulation is low, but it should be confined to such meaning. Gravity resistance is a more fundamental term underlying the phenomenon of blood ptosis and the opposite of blood ptosis as well.

In interpreting the scale it would be advisable at the outset to relieve the mind of the notion that 100 is normal and that 0 means no gravity resistance. Such is not the case.

<sup>2</sup> Clinical Significance of Postural Changes in the Blood-pressures, *AM. JOUR. MED. SC.*, December, 1919, No. 6, clviii, 573.

Blood-pressure--Increase.

Heart-rate.	50 to 49	48 to 47	46 to 45	44 to 43	42 to 41	40 to 39	38 to 37	36 to 35	34 to 33	32 to 31	30 to 29	28 to 27	26 to 25	24 to 23	22 to 21	20 to 19	18 to 17	16 to 15	14 to 13	12 to 11	10 to 9	8 to 7	6 to 5	4 to 3	2 to 1
Decrease.																									
- 8 to -12	215	210	205	200	195	190	185	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95
- 4 to - 8	210	205	200	195	190	185	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90
0 to - 4	205	200	195	190	185	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85
Increase.																									
0 to 4	200	195	190	185	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80
5 to 8	195	190	185	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75
9 to 12	190	185	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70
13 to 16	185	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65
17 to 20	180	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60
21 to 24	175	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55
25 to 28	170	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50
29 to 32	165	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45
33 to 36	160	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40
37 to 40	155	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35
41 to 44	150	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30
45 to 48	145	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25
49 to 52	140	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20
53 to 56	135	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15
57 to 60	130	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10
61 to 64	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5
65 to 68	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0
69 to 72	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	- 5
73 to 76	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	- 5	-10
77 to 80	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	- 5	-10	-15

There are normal men and women with an index as low as 50 and abnormal cases with ratings as high as 120, just as there are normal persons with a pulse-rate from 50 to 80 and many sick persons with the same range. There is no one normal blood-pressure. A patient with arteriosclerosis that has carried a systolic pressure of 200 for several years will give us good cause for alarm when his pressure falls to 120. This is a supposedly normal record, but here it probably means the final break-down of his circulation. Similarly one must not expect to find any one gravity resistance index to be a normal. We can safely say, however, that most persons in good health show an index of from 60 to 100, that a record of over 80 in a person in poor health needs explanation and that a cause should be sought for a record below 50. A record below zero in the minus range is explicit evidence of an impaired circulation, a toxic state or acute severe physical disturbance.

**Conduct of the Test.** Splanchnic vasotone is measured in the following manner: The sphygmomanometer is adjusted over the brachial artery and the patient is placed on a comfortable couch

RESISTANCE VALUE.

Crampton Value.)

Blood-pressure—Decrease.

0	1 to 2	3 to 4	5 to 6	7 to 8	9 to 10	11 to 12	13 to 14	15 to 16	17 to 18	19 to 20	21 to 22	23 to 24	25 to 26	27 to 28	29 to 30	31 to 32	33 to 34	35 to 36	37 to 38	39 to 40	41 to 42	43 to 44	45 to 46	47 to 48	49 to 50
80	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35
85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40
75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50
70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55
65	60	55	50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60
60	55	50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65
55	50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70
50	45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75
45	40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80
40	35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85
35	30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90
30	25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95
25	20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100
20	15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105
15	10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110
10	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110	-115
5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110	-115	-120
0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110	-115	-120	-125
-5	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110	-115	-120	-125	-130
-10	-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110	-115	-120	-125	-130	-135
-15	-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110	-115	-120	-125	-130	-135	-140
-20	-25	-30	-35	-40	-45	-50	-55	-60	-65	-70	-75	-80	-85	-90	-95	-100	-105	-110	-115	-120	-125	-130	-135	-140	-145

with a low pillow. The heart-rate is counted by quarter minutes and a gradually decreasing rate is usually observed. Counting should continue until two successive quarter minutes are the same; this is multiplied by four and recorded. The systolic pressure is then taken preferably by auscultation. The patient stands, the heart-rate is counted as before until it reaches the "standing normal," when it is recorded, and the blood-pressure is then taken.

EXAMPLES.

CASE I.—Male, aged twenty-eight years. Physical director; ex-lieutenant, U. S. Marines.

Horizontal	Systolic.	Diastolic.	Pulse-rate.
Vertical . . . . .	125	81	64
	140	92	76
Difference			
Index . . . . .	+15	+11	+12
			+105

Referring to the scale we will find a column under blood-pressure increase, the one headed by the figures 16, 15; following down this

column until we come opposite the line marked on the left of the scale 9 to 12 we find the index 105, which is the desired value for the above record.

CASE II.—Woman, aged fifty-seven years. Uterine fibroid.

	Systolic.	Diastolic.	Pulse-rate.
Horizontal . . . . .	113	80	68
Vertical . . . . .	130	78	68
	<hr/>	<hr/>	<hr/>
Difference . . . . .	+17	-2	0
Index . . . . .			+120

CASE III.—Male, aged fifty-two years. Neurasthenic.

	Systolic.	Diastolic.	Pulse-rate
Horizontal . . . . .	120	50	88
Vertical . . . . .	105	55	96
	<hr/>	<hr/>	<hr/>
Difference . . . . .	-15	+5	+8
Index . . . . .			+30

CASE IV.—Woman, aged forty-five years. Tuberculosis.

	Systolic.	Diastolic.	Pulse-rate.
Horizontal . . . . .	108	66	90
Vertical . . . . .	82	54	110
	<hr/>	<hr/>	<hr/>
Difference . . . . .	-26	-12	+20
Index . . . . .			10

CASE V.—Woman, aged fifty-three years. Dementia.

	Systolic.	Diastolic.	Pulse-rate.
Horizontal . . . . .	184	88	80
Vertical . . . . .	100	70	82
	<hr/>	<hr/>	<hr/>
Difference . . . . .	-84	-18	+2
Index . . . . .			135

These few cases are selected to illustrate the wide gamut of index value from the plus 120 to minus 135. The highest record here given (Case II) is that of a case of uterine fibroid—weak, anemic, irritable; clearly a pathologic overactivated resistance, where we would expect from other symptoms the reverse. This rare condition appears to occur most frequently where there is abdominal pain and irritation apparently nagging the sympathetic system into an abnormally active reaction to the standard physiologic load.

CASE I.—The athletic young man is simply tingling with vigor and his circulatory resistance is more than commonly active. The best boxers, wrestlers, runners and long-distance bicycle riders when in good condition show a value of from 80 to 100.

CASE III.—Is a typical neurasthenic with a typical fall in systolic pressure and a rise in pulse-rate (a little less than common),

a mild degree of blood ptosis. Neurasthenics most commonly show a record of plus 50 to minus 10.

CASE IV.—Is a typical picture of the pretubercular state. These cases almost always show a systolic pressure of 100 to 110 horizontal, and a fall of from 10 to 25 mm. on standing—the diastolic also falls, but following custom, it falls less than the systolic. This class of cases usually show an index of from plus 30 to minus 30.

CASE V.—This is an extreme blood ptosis indicating a profound disability of the nervous control of the circulation which curiously was structurally intact. This case was followed for some weeks and retested frequently and her indices varied from minus 80 to minus 150.

Zero and minus records are not uncommon. They may be obtained by any physician who can and will keep a very sick patient on his feet long enough to take the necessary readings. They occur, however, in ambulant cases where the circulation has become habituated to its disabilities. The lowest reading the writer has recorded is as follows:

CASE VI.—Woman, aged fifty years. Diabetes.

	Systolic.	Diastolic.	Pulse-rate.
Horizontal . . . . .	178	84	80
Vertical . . . . .	88	50	96
Difference . . . . .	—90	—26	+16
Index . . . . .			165

	Systolic.	Diastolic.	Pulse-rate.
Retest, third day after.			
Horizontal . . . . .	152	86	80
Vertical . . . . .	80	58	88
Difference . . . . .	—72	—28	+8
Index . . . . .			110

**The Gravity Resistance in Various Diseased Conditions.** Gravity resistance records were taken on every patient entering the sanitarium. The average of the indices for each class of cases, with the number of cases in each class, is given in the table on p. 728.

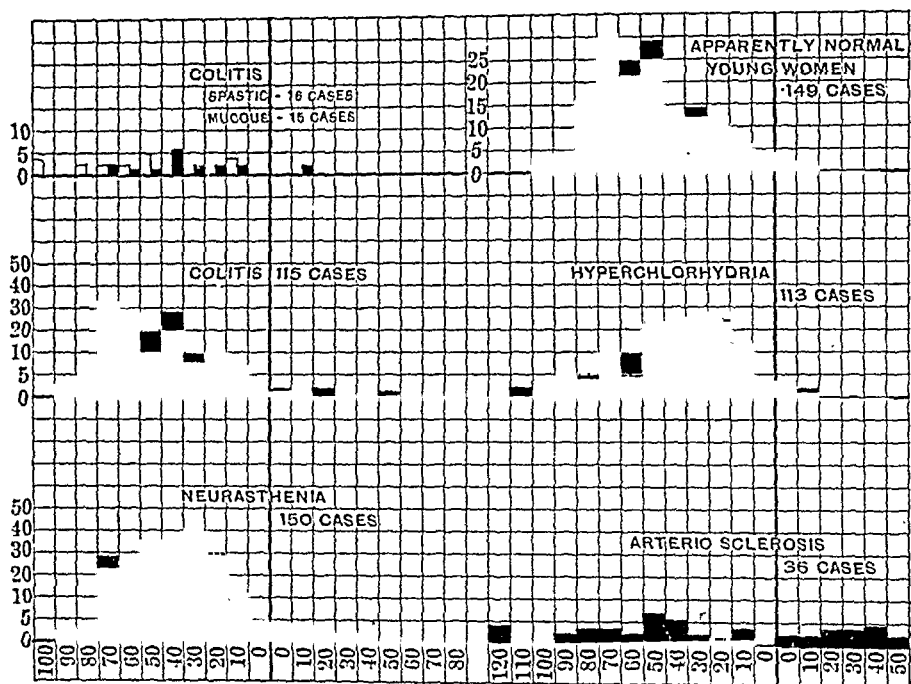
From these figures it is apparent that there is a tendency for certain diseased conditions to be associated with indices that are higher or lower than others. Differences in averages, however, grade by very easy steps from one condition to another, and it is apparent that the hopeful clinician who sees in the gravity resistance index an invariable diagnostic sign will be disappointed.

The importance of the above schedule is at present somewhat limited. The statistical method may be applied to a still larger number of cases and we may be able to state with certainty, for instance, that hyperthyroidism exhibits a standard average index of 60, while migraine shows a value of 52 and pellagra 40. This

might possibly be of importance to the practising physician, but of undoubted importance to the clinician is the fact that the index varies greatly in each diseased condition. For example, in a series of nine cases of paralysis agitans the highest index is 85, the lowest 15; of 105 neurasthenics, the highest is 90 and the lowest is — 165. We venture to suggest that these tremendous differences in circulatory function are quite as important to the physician and to the patient as the diagnosis itself, and possibly more so, for they give one indication at least of *how sick he really is*.

Number of cases.	Diseased condition or most prominent symptom.	Index.
22	Rheumatism	78.8
7	Hyperthyroidism	60.7
12	Irritability	60.7
12	Hay fever	57.0
5	Cholecystitis.	57.0
9	Dysmenorrhea	53.8
37	Obesity	53.3
6	Hypothyroidism	52.0
54	Migraine	51.0
3	Arthritis	51.0
15	Colitis (spastic)	51.0
65	Secondary anemia	49.0
17	Nephritis	49.0
12	Carcinoma	48.0
8	Cystitis	48.0
13	Hysteria	48.0
4	Gastric ulcer	48.0
11	Cystocele	47.0
20	Mitral stenosis	47.0
5	Asthma	46.0
115	Colitis	46.0
23	Hypochlorhydria	46.0
46	Asthenia	45.0
28	High blood-pressure	45.0
105	Neurasthenia	45.0
83	Hyperchlorhydria	43.0
7	Sciatica	42.0
6	Neuralgia	41.0
7	Duodenal ulcer	40.0
2	Vertigo	40.0
34	Arthritis deformans	39.0
25	Lues	39.0
25	Neuritis	39.0
15	Colitis (mucous)	38.0
54	Myocarditis	38.0
3	Pellagra	38.0
37	Arteriosclerosis	37.0
21	Mitral insufficiency	36.0
39	Insomnia	33.0
17	Pulmonary tuberculosis	33.0
12	Chronic appendicitis	31.0
8	Paralysis agitans	31.0
8	Albuminuria	28.0
24	Mental depression	25.0
2	Paresis	17.5
15	Splanchnoptosis	12.6
14	Cardiovascular renal complex	14.6
6	Angina	-3.0

A preliminary study of the distribution of the indices in disease groups, reveals the fact that in the case of some diseases there is little variation, in others there is much.



Reference to the charts will indicate that 115 neurasthenia cases are grouped closely about plus 20 to plus 70 range, while 36 arterio-sclerosis cases range loosely from plus 120 to minus 50. In 115 colitis cases there appears distinct evidence of bimodality in the plotted curve, indicating the presence of two groups of colitis cases reacting differently in gravity resistance. One group centers about plus 60 and 70 and another has an indication of a mode about 40. The distribution of a few cases of colitis, one diagnosed as mucous and the other as spastic, plotted above the colitis curve, suggests the possible explanation that spastic colitis cases show a high gravity resistance and other colitis cases lower.

The distribution of cases of arteriosclerosis also suggests the inclusion of subgroups under one diagnostic head. In this case, there are three groups suggested, centering respectively at plus 120, plus 60 and minus 40. It is quite possible that there are three corresponding disease conditions coinciding with these modes. It is quite certain that those cases of arteriosclerosis with indices below zero are suffering from a severe disability of the gravity resisting forces of the circulation. It is equally clear that the four cases with indices of 120 and over have their gravity resisting forces in a hyper-efficient state. The clinical significance of these striking facts is not as yet known. The foregoing is merely a preliminary entrance into a most fascinating and unworked field in medicine.



**Physiologic and Other Clinical Variations of Gravity Resistance Ability.** In the experience of the author, young men in good physical condition have high indices, running, as a rule, from 70 to 100. Dr. R. Tait McKenzie, of the University of Pennsylvania, reports from records taken from the University of Pennsylvania crew the average of 116 observations:

	Systolic.	Pulse-rate.
Horizontal . . . . .	116.6	77.2
Vertical. . . . .	115.5	85.2
Difference . . . . .	—1.9	+8.0
Index . . . . .		65

This index is lower than could be expected in young men prepared to enter a severe test of endurance. It reflects, however, exactly the condition of the circulation at the time. It is quite possible that men in athletic training become fatigued in circulatory control, a fact which may account for many hitherto unexplained defeats in athletic contests.

Under standardized conditions this value is an accurate indication of the "condition" of the athlete.

Mr. C. H. McCloy, instructor in physiology of exercise in a Young Men's Christian Association, and an athletic coach (reports unpublished), says that after he had standardized his athletes by establishing an initial correlation between their athletic performance and the index, it proved an exceedingly reliable measurement for the type of condition which varies from day to day.

"I could tell with fatal accuracy this individual's condition relative to his general condition at the time. If there was any doubt as to which individuals should play the basket-ball game (many thus of almost equal scale and endurance), this test was of exceeding value in determining relative condition of this individual.

"I found, furthermore, that the condition producing a high index was not only conducive to good performance, as to endurance, nervous speed and strength, but was exceedingly accurate in determining skill as well. Thus, for example, I have become somewhat able to predict accuracy and inaccuracy in basket-shooting for basket-ball players. In testing baseball pitchers I was even enabled to predict at times, with relative certainty—after I had experimented with the individual and gotten his personal equalization—about how many hits and runs would be made off of him when I knew the general ability of the other team.

"The explanation of all of this seems to me to be tied up very closely with the relationship of splanchnic tension to the present condition of the individual. The presence of fatigue poisons, results of auto-intoxication of any sort or of latent or active infection would show itself immediately in lack of splanchnic tone and power of recovery upon resuming the upright posture."

In other words, he found that though his athletes differed from each other in index, yet their variations from their own individual standards were strikingly parallel to motor efficiency of the athletic type. In my own earlier work with athletes I had the same experience, but not to the degree reported by McCloy.

Aviators have been tested at the Experimental Laboratory of the Air Service at Mineola, New York, under Major Edward C. Schneider. He has communicated to the author data (as yet unpublished), showing a striking coincidence of values and the results of various other tests. He grouped the aviators into four classes in accordance with their reaction to medical and psychologic tests, including the rebreathing low oxygen test, the rotation test, reaction time, etc., and used the author's index.

His four classes and their corresponding average gravity resistance is given as follows:

Aviation class.	Index.
AA . . . . .	88.75
A . . . . .	68.25
B . . . . .	57.00
C (5 cases only) . . . . .	68.13

Schneider also records a fall in value in 65 per cent. of cases after flying; in some cases this amounted to 30 per cent. The indices clearly suggest a correlation with physical condition.

Norris and Lane have reported a brief study of "vasotone," using our method,<sup>3</sup> with the following results:

	Average.	Lowest.	Highest.
Class A (10 heart cases):			
Before compensation . . . .	62.5	35.0	75.0
After compensation on getting out of bed after three or four weeks' rest and treatment . .	93.6	80.0	100.0
Class B (58 convalescent cases):			
On classification as convalescents after illness . . . .	45.9	10.0	67.0
After four weeks' additional treatment . . . . .	81.0	40.0	100.0
Class C.:			
A group of apparently well persons . . . . .	79.3	55.0	100.0

The high record 93.6 made by the heart cases after rest indicates the striking improvement in what is usually called "general condition" under treatment. It also indicates the fact that the structural and functional factors in the circulation may vary independently, and where the structural factors cannot be changed the functional may.

In a most clear-cut report of an excellently planned investigation, Smith,<sup>4</sup> of Los Angeles, using the author's scale, relates the "vaso-

<sup>3</sup> Arch. Diag., July, 1917.

<sup>4</sup> Jour. Am. Med. Assn., No. 3, vol. xi.

tonic" condition of a series of 500 recruits, which passed through his hands. He gives an average index of 86.9 for 500 men. He also observed low indices, plus 52, in a recruit two days before he became sick with measles and plus 92 on recovery. This recalls a case of a young athlete, found upon examination for admission to college athletics to have inexplicably low indices, and reporting sick a day or so later. The author has previously reported cases of this kind.<sup>5</sup> It is clear that one can only stumble on these cases occasionally in the course of routine examination. It is quite clear that a sudden drop in index may mark the *onset of acute disease before any other symptom is present.*

An interesting case that has come under the author's notice is that of a colleague at the Battle Creek Sanitarium who had been used as a subject for a study of vasotone variations.

Date.	Hour.	Feelings.	Systolic.	Diastolic.	Pulse.	Index.
Aug. 20, 1919	8.45 A.M.	Fine	H. 170	110	80	85
			V. 173	108	84	
			—	—	—	
Aug. 21, 1919	9.10 A.M.	Depressed	+3	-2	+4	55
			H. 176	104	80	
			V. 168	116	84	
Aug. 22, 1919	9.30 A.M.	Good	—	—	—	100
			-8	+12	+4	
			H. 170	105	84	
Aug. 24, 1919	9.00 A.M.	Dizzy, nauseated and feeling ill	V. 180	120	84	-20
			—	—	—	
			+10	+15	0	
			H. 134	80	84	
			V. 106	80	108	
			—	—	—	
			-28	0	+24	

This patient was sick during the day and for some time afterward with a digestive and nervous collapse. He returned to his usual range of index, 40 to 90, on recovery.

In this case it will be noted that there was an actual fall of the vertical pressure. This is not always the case, for the index may fall as the pressures rise. The same subject showed the following record:

Date.	Hour.	Feelings.	Systolic.	Diastolic.	Pulse.	Index.
Aug. 14, 1919	3.35 P.M.	Reste after nap	H. 166	110	68	90
			V. 171	105	72	
			—	—	—	
Aug. 14, 1919	5.05 P.M.	Excited; "rushed"	+5	-5	+4	85
			H. 184	123	66	
			V. 180	115	66	
Aug. 14, 1919	6.10 P.M.	Still rushed and excited	—	—	—	35
			-4	-8	0	
			H. 188	115	68	
			V. 172	118	72	
			—	—	—	
			-16	+3	+4	

<sup>5</sup> Med. News, op. cit.

In this instance, excitement, work and the tension of hurry raised the systolic pressure (especially the horizontal) but progressively lowered the gravity resistance. These records illustrate the fact that gravity resisting ability varies independently of the actual blood-pressures.

The index has been used by Goldberger,<sup>6</sup> under the writer's direction, to ascertain the effect of work days and holidays upon "vaso-tone." The following results were obtained:

	Number of cases.	Average change.	Greatest increase.	Greatest decrease.
Fatigue of one school day . . .	13	-9.3	+10.0	-27.5
Recuperation over week-end . . .	13	+1.7	+37.5	-40.0
Recuperation during Easter holidays . . . . .	13	+3.6	+27.5	-37.5
Depreciation January 22 to March 25 . . . . .	13	-7.3	+40.0	-32.5
Recuperation, 53 cases, summer vacation, June 24 to September 15.				
		Average change.		
First group, nine to ten weeks spent in country . . . . .				+13.7
Second group, four to eight weeks spent in country . . . . .				+14.3
Third group, one to four weeks spent in country . . . . .				+8.3
Fourth group, taught summer school . . . . .				-20.8
Fifth group, ill during the summer . . . . .				-16.7

These figures present striking pictures of the effect of rest and recuperation in contradistinction to work and illness and open a primary field of research in industry.

Another valuable research which throws light upon the effect of working conditions upon efficiency has been made by the New York State Ventilation Commission.<sup>7</sup> They made thirteen different physiologic records, including the index, and report as follows:

"A very high room temperature, such as 86° F., with 80 relative humidity, produces slight but distinct elevation of body temperature, an increase in reclining heart-rate, an increase in the excess of standing over reclining heart-rate, a very slight lowering of systolic blood-pressure and a marked fall in the "Crampton value."

The final summary is as follows:

Temperature.	Air.	Crampton index.
68° F.	Still	+60.0
75° F.	Still	+45.0
86° F.	Stirred by fans	+40.0
86° F.	Still	+35.0

This indicates the tonic effect of cool air and the blood ptosis producing effect of hot air, particularly when still.

*Tobacco.* The effect of tobacco upon the gravity resistance ability is often quite marked. A single subject was carefully stand-

<sup>6</sup> Teachers' Vitality as Indicated by the Blood-ptosis Test, New York Med. Jour., April 29, 1916.

<sup>7</sup> Some Results of the First Year's Work of the New York State Ventilation Commission, Am. Jour. Public Health, No. 2, vol. v.

ardized for a period of a week. He was thirty-five years old, in the diplomatic service of the United States, a neurasthénic and had been an occasional heavy smoker, when called upon for long-continued work. His customary gravity resistance index was +20 to +60. He had not smoked during the previous week.

	Systolic.	Diastolic.	Pulse-rate.	Index.
Room temp. 73° at 11.00 A.M. . . . .	H. 112 V. 106	60 74	72 100	
	— —6	— +14	— +28	+30
Cigarette given 11.20 A.M. . . . .	H. 134 V. 114	75 80	92 110	
	— —20	— +5	— +18	+5
Dizzy, asked to lie down, 11.30 A.M. . . . .	H. 114 V. Below 70 (by palpation. No sounds heard). Patient would not or could not stand. Insisted on lying down; profuse perspiration; nauseated.			

This is the clear picture of tobacco sickness and is typically a blood ptosis. Unfortunately the observer could not get the pulse-rate, or follow the systolic pressure down below 75. The index was probably between minus 60 and minus 80, and going down. The experiments were made in the bath treatment room, with the temperature at 73° and the humidity over 80. This is noteworthy, for the temperature was lowered to 57° to 60° the next day and strikingly different results were obtained, as follows:

	Systolic.	Diastolic.	Pulse-rate.	Index.
11.00 A.M., temp. 57° . . . . .	H. 132 V. 134	84 86	72 72	
	— +2	— +2	— 0	80.0
11.13, lit cigarette . . . . .	...	...	78	
11.13½ . . . . .	...	...	88	
11.14½ . . . . .	...	...	92	
11.15½ . . . . .	H. 146 V. 170	90 104	96 96	
	— +24	— +14	— 0	135.0
11.21 . . . . .	H. 148 V. 162	90 98	88 88	
	— +14	— +8	— 0	110.0

The resistance was quite high, (80) before smoking, due to the temperature effect, quite in accord with the New York State Ventilation Commission findings. Under this stimulus the cigarettes acted

very differently from the day before. The systolic pressure, 20 points higher than the day before to begin with, rose abruptly 14 mm. in the horizontal position and 26 in the vertical, with both diastolic pressures and pulse-rates increasing, whereas, under the hot, heavy, humid atmosphere of the day before, the bottom literally dropped out of the pressures. This experiment, although unreported, is reported because of its striking demonstration of variations in gravity resisting ability. It is, of course, only a single case and should be evaluated as such. It is submitted in the hope that others may be in a position to make similar tests.

In the opinion of the writer the subject was sensitized to the effect of tobacco because of his previous overindulgence and had developed a tolerance to its toxic effects. This tolerance was broken down by the removal of its customary stimulation and left the system peculiarly sensitive to the effect of the tobacco.

#### RECORDS BEFORE AND AFTER TONSILLECTOMY.

Case No.	Before operation.	Number of days after operation.				
		1	2	3	4	5
I . . . . .	70	55	50	50	60	
II . . . . .	85	25	20	65	80	75
III . . . . .	105	60	..	..	..	60
IV . . . . .	40	50	40	55	50	
V . . . . .	55	45	30			
VI . . . . .	50	35	50			
VII . . . . .	75	90	75	50	55	80
VIII . . . . .	30	20	40	25	35	30
IX . . . . .	80	95	60	30	30	20
X . . . . .	75	55	70	80	90	
Average . . . . .	66.5	53	48.3	50.7	57.4	53.0

These few cases show certain points of interest. The average show a decrease after operation, the lowest point resting on the second day. The reaction of individuals varies. Cases IV, VI and VIII were low and lost little in circulatory power. The highest records, notably Cases II and III, lost the most. Two cases (VII and IX) actually increased in resistance power only to fall to low records on the third day. Case VII recovers on the fifth day while Case IX continues low. It is of interest to note that he suffered from kidney disease and was sick enough to be returned to the hospital on the fifth day (with an index of 20) for further treatment.

There have appeared in medical reports from time to time, in medical literature, various statements as to the reaction of the blood-pressures on rising from the horizontal to the vertical position. For example: "The systolic always falls on 'rising,'" "the diastolic always rises on standing;" "the pulse pressure always decreases on rising from the horizontal to the vertical." The action of the systolic pressure and the reasons for the action are discussed in this

communication. The bare facts from over seven hundred cases are given below:

# EFFECT OF RISING FROM HORIZONTAL TO VERTICAL POSITION.

Patients entering the Battle Creek Sanitarium.

	Number of cases.	Per cent.	Total cases.
Diastolic:			
Rises . . . . .	403	54	
Falls . . . . .	336	46	739
Systolic:			
Rises . . . . .	109	15	
Falls . . . . .	639	85	739
Systolic rises; diastolic rises . . . . .	83	11	
Systolic rises; diastolic falls . . . . .	26	4	
Systolic falls; diastolic rises . . . . .	320	43	
Systolic falls; diastolic falls . . . . .	310	42	739
Pulse-pressure increases . . . . .	78	11	
Pulse-pressure remains the same . . . . .	70	9	
Pulse-pressure decreases . . . . .	593	80	741

These figures will hold true for this class of cases. The proportions will vary from these standards in every group of cases studied, depending on the degree of illness and its nature.

*Summary.* 1. The horizontal and vertical blood-pressures may differ greatly in the same individual.

2. A rise in systolic pressure on standing indicates efficiency in the gravity resisting ability of the circulation; a fall, the reverse.

3. The increase in heart-rate on standing indicates inefficiency in the gravity resisting ability of the circulation in proportion to the increase.

4. Taking both influences into consideration, an index may be determined for convenient use.

5. This index is lowered by various influences among which are fatigue, toxins, the approach of disease and disease itself.

6. This index may be high in good health and also in some diseased conditions.

7. The index may prove helpful in estimating the extent illness is damaging the circulation in the course of disease and in estimating the progress of recovery.

8. This index may indicate the fatigue and the variations of condition in an athlete.

9. The normal range of this value is approximately from 50 to 100, although records in this range may be given by sick persons, but high records in sick persons are probably evidences of pathologic overtone.

10. Records below zero are evidences of great lack of circulatory power.

11. Comparison of records of two individuals may or may not

give much information. Successive records on the same case may give more.

12. The customary single recording of the blood-pressure in one position gives no information as to the gravity resisting function of the circulation.

## PERNICIOUS ANEMIA: A STUDY OF ONE HUNDRED AND FORTY-EIGHT CASES.

BY JAMES G. CARR, M.D.,

CHICAGO, ILL.

THE study embraces a total of 148 cases discharged from the Cook County Hospital under the diagnosis of pernicious anemia, which may be divided into two main groups: (1) those in which the diagnosis was purely clinical, and (2) those in which the diagnosis was confirmed or corrected at autopsy. There were 22 of these latter. Of the other cases, 126 in number, 112 may be accepted, on the basis of the clinical study, as pernicious anemia; another group of 14 cases is made up of those which were discharged, with a question as to the diagnosis. Of the 112 cases accepted as clinically pernicious anemia, 26 will be discussed as a separate group, since they presented, as a major manifestation, the important group of symptoms denoting involvement of the spinal cord. There are therefore, 86 cases left to be studied as cases typical of pernicious anemia.

Certain features, however, may best be discussed with reference to their occurrence on the basis of the total figures. Of the total number of cases, 134 in number, clinically regarded as pernicious anemia, 94 occurred in males and 40 in females, an incidence of 70 per cent. and 30 per cent. respectively. Of the 134 cases, 67 died in the hospital, 67 left the hospital: some of them no better, many improved and a few recorded as worse and leaving at their own request. The number of histories actually studied was 161; nine of the patients had records of two periods in the hospital and two each had three histories. The histories used covered a period from 1912 to the present time. Seven of the patients were under thirty years of age; 31 were between thirty and forty; 39 were between forty and fifty; 36 between fifty and sixty; 35 over sixty. Only 6 of the cases occurred in negroes; evidently the incidence of the disease in negroes is low; the percentage occurrence here is slightly under 5; it is safe to assume that the percentage of negro patients in the County Hospital is at least twice this figure. So far as statements could be obtained the disease had lasted, prior to admission to the hospital, less than six months in 28 cases, between six months and two years in 40 cases and more than two years in 34 cases.



We will consider first the 86 cases, diagnosed as pernicious anemia, in which there were no cord symptoms or in which such symptoms were minor. A few symptoms were repeated with monotonous regularity. The symptoms of onset, as described upon the patient's admission to the hospital, may be listed as follows: Weakness, progressive in character, was mentioned 66 times; dyspnea, especially marked on exertion, 43 times; edema of the feet, in most cases worse at night, 34 times; gastric disturbances were frequent; vomiting, which occurred in 32 cases, was characterized by the absence of any regularity or relation to the taking of food; in some patients vomiting had occurred at rather long intervals and persisted for several days at a time; others would vomit "everything they ate" for weeks at a time, and others, now and then, without any apparent cause; in 10 of the cases it was stated that no blood had been vomited; in only 1 was there a history of bloody vomitus; and 20 patients expressly stated that no vomiting had occurred. Two reported themselves as very hungry; in 13 the appetite was good and 30 others made complaints of various degrees of absence of appetite. Sixteen complained of a fulness or dull pain in the abdomen; in 4 cases this was aggravated by eating. In 17 the bowels had been regular; in 17 there was constipation; in 12 diarrhea and in 4 an alternating constipation and diarrhea. Loss of weight was mentioned 26 times; in 24 of these a definite figure was given; the average loss of weight was thirty-two pounds; in 8 cases it had amounted to more than forty pounds. Dizziness was a symptom in 20 cases; palpitation of the heart in 16; headache in 13. Numbness, with or without coldness of the extremities, was an early symptom in 19 cases; cramps and shooting or dull pains in the legs were noted 6 times. The pallor was only mentioned 10 times, and in only 3 cases did the patient speak of the yellow color of the skin. Double vision had occurred once; other infrequent nervous symptoms were drowsiness, tinnitus, nervousness, irritability and insomnia. Only 3 patients gave a history of fainting. Epistaxis was mentioned 6 times; hemoptysis in 2 other cases. A sore-mouth occurred in only 4 cases. Fourteen complained of cough and 6 of night-sweats.

One patient stated that his mother had died of pernicious anemia; there was nothing of importance in the family or personal histories nor any evidence of relationship to past diseases.

On physical examination the "lemon yellow" color of the skin was noted 36 times; "jaundice," 8. Whether or not the yellowish color was incorrectly interpreted as "jaundice" cannot be said. In every instance the pallor of the skin, mucous membrane and scleræ was noted. Carious teeth were mentioned 32 times and pyorrhea 19; while atrophy of the lingual papillæ was only mentioned twice. It seems likely that the oral and lingual mucous membrane was not carefully examined. The cardiac findings were of special interest;

systolic murmurs were noted at the apex alone in 25 cases; at the base alone in 8 and at both base and apex, or over the entire precordium, in 21—a total of 54 cases. To these must be added 3 cases in which a presystolic murmur was described at the apex; another with a presystolic thrill and murmur and a systolic murmur at the apex; another with a diastolic murmur at the base (in which an autopsy one year later showed no organic cause for the murmur); another with a systolic at the apex and a diastolic along the left border of the sternum; a total of 60 cases which showed cardiac murmurs. The presence of a murmur may be regarded as one of the most constant findings of pernicious anemia. In this series it was present in 70 per cent. of the cases. Cardiac irregularities were uncommon—only 3 were described; these were probably of the type known as premature ventricular contractions. The cardiac outlines were recorded 36 times; in 28 of these the area of cardiac dullness was increased. Dilatation as a finding in pernicious anemia is equally as common as the presence of murmurs. The blood-pressure estimation varied from a systolic of 84 to one of 176; of 55 readings only 5 were above 150; 32 were below 115, 10 of these below 100. In view of the fact that the disease is one of adult life, it may be concluded that a low blood-pressure is the rule, and a blood-pressure higher than the normal for the age is an unusual finding in a case of essential anemia. The diastolic pressure varied from 40 to 90; of 50 readings, 35 were below 70; the average pulse-pressure was 53. We can regard the blood-pressure of pernicious anemia as characterized by a low systolic reading, a disproportionately low diastolic and an unusually high pulse-pressure.

The liver was palpable in 35 cases; 10 times it was stated to be as much as three finger-breadths below the costal arch; the spleen was palpated 19 times; general adenopathy was recorded but 4 times. Edema of the extremities was noted 23 times; extensive edema 4 times. The pulmonary findings were negligible; in 7 cases subcrepitant rales over both bases posteriorly were described; in 2 cases "coarse rales throughout the chest;" in another, dullness with increased tactile and vocal fremitus over both apices. A few cases presented the findings of old healed apical tuberculosis.

In 23 cases the temperature was never over 99; in 32 it usually ran from 99 to 100; in 12 from 100 to 101; in 8 over 101 at least once; this does not include some cases with terminal temperature; of 75 cases, fever was present at some time in 52. The pulse was frequently 100 or over in 29 cases. The pupils were noted as being normal in 77 cases; in 7 they reacted normally but showed irregularity or inequality. Only 2 of the patients had epistaxis while in the hospital. The reflexes were noted as normal in 57 cases; in 3 they were exaggerated; in 7 the patellar and Achilles reflexes were absent; in 1 other the patellar was absent on one side.

Sputum examinations were made in 10 cases; all were negative

for tubercle bacilli. For the other laboratory findings, aside from the blood counts, we will give the figures from the total of cases diagnosed during life as pernicious anemia without qualification, 134 in number. The Wassermann test on the blood is recorded for 46 cases; 42 were negative, 3 were 4+ positive, another, 1+. The test on the spinal fluid was negative 14 times. Gastric analyses were recorded in 57 cases; 53 of these showed no free HCl; 1, a free HCl of 2; 2 others of 7; the other case showed so much blood that acidity could not be tested for; of the 56 cases tested, 29 showed a total acidity under 10, 21 between 10 and 20, and 6 over 20. In 93 per cent. of the cases examined the stomach contents showed no free HCl; the achylia is obviously an important clinical symptom of pernicious anemia. Of 53 urine examinations taken at random 37 showed a specific gravity of less than 1015; 24-hour specimens from 8 patients showed a total of more than 1500 c.c. in 7 instances; in the other the amount was 350 c.c. The urine was otherwise negative in 41 cases. Albumin was present without casts in 7 instances; with hyaline and granular casts in 2; a few hyaline casts were noted twice; a few red cells in the remaining case. We believe these conclusions are warranted: The usual urine of pernicious anemia is increased in amount and of a low specific gravity; albumin is not often found and the constant presence of albumin and casts makes the case questionable, speaks against the diagnosis of pernicious anemia and for the existence of a nephritis as the fundamental disease producing the anemia. Ophthalmoscopic examination was recorded 17 times; in 2 instances the eye-grounds were negative; in 6 there were hemorrhages; in 3 the disk was "hazy;" the eye-grounds were noted as pale 5 times; there was bilateral "beginning optic atrophy" once. In 45 cases examinations of feces were made; in 24 of these search was made for ova or parasites but none were found, and all the examinations were negative for pus and blood.

We come now to a consideration of the blood counts. The lowest erythrocyte count was 320,000. There were in all 6 patients with red counts below 500,000; 2 of these recovered sufficiently to leave the hospital. Thirty-six patients had erythrocyte counts below 1,000,000; 19 of these improved sufficiently to leave the hospital; thus the percentage of deaths in the hospital was 47. The patients with erythrocyte counts of 1,000,000 or above numbered 50; of these 14 died in the hospital, a mortality of 28 per cent. The prognosis is made decidedly worse as the red cells diminish. Only 8 of the cases had initial counts of more than 2,000,000; in this group there were 2 deaths; 1 occurred after a profuse hemorrhage from the nose and mouth; the second case had been admitted to the hospital with a history of hemorrhages from the nose, stomach and bowels; his color index was 0.5; no hemorrhages were noted in the hospital but he failed rapidly. The color-index was 1+ in 74 cases and below 1 in 12. Nucleated red cells were described in 31 cases.

The highest leukocyte count was 30,000; in this case there had been pain over the upper sternum for one month; this was intermittent and worse on exertion; there was swelling of the abdomen; hemorrhoids were present; there were nausea and vomiting, especially in the morning; the color-index was 0.83; this case was distinctly questionable. The next highest white count was 13,900; only 3 counts over 10,000 occurred; there were 41 counts below 5000, a percentage of 45, and 16 of 3000 or below; the lowest count was 1100. In 24 cases there was a distinct relative lymphocytosis; in 23 the differential white count was normal; in 39 it was not noted. Thus when a differential count was made a relative lymphocytosis was present in a majority. The conclusion seems justified that pernicious anemia is characterized by a low white count, with a tendency to a leukopenia and a relative lymphocytosis. Fourteen cases, or 58 per cent., of relative lymphocytosis occurred among the 36 cases in the group characterized by red counts of less than 1,000,000; 7, or 50 per cent., of these died. It seems that the appearance of this relative lymphocytosis is of grave prognostic import; only 2 of these 14 cases showed total counts over 6000; the condition really signifies an absolute decrease of the polymorphonuclears, which is significant of failure on the part of the blood-making organs to meet the constant and excessive demands on their function.

A few cases deserve special mention in our consideration of the blood counts:

F. G., aged thirty-two years, was in the hospital from June 1 to September 11, 1915. On admission his blood examination showed hemoglobin 22, erythrocytes 990,000, leukocytes 3150; all the pathologic forms of erythrocytes were present. August 30 examination showed hemoglobin 75, erythrocytes, 4,640,000, leukocytes 8200, and a few poikilocytes. He had been treated with dilute hydrochloric acid, sodium cacodylate and enemata of normal salt solution, 1 gallon every morning.

H. O., aged fifty-six years, was admitted to the hospital June 13, 1914. He was irrational and very sick. Blood examination showed 560,000 erythrocytes, 6200 leukocytes, color-index 2, small lymphocytes 44, large lymphocytes 10, polymorphonuclears 42. All forms of pathologic reds were present. She was discharged July 25, 1914, at which time the examination showed 80 per cent. hemoglobin, 4,040,000 erythrocytes and color-index 1. The stained specimen was normal. She was treated with Fowler's solution.

A somewhat similar case was that of W. C., aged forty-two years, admitted to the hospital May 6, 1916, and discharged July 3, 1916. On examination his blood showed hemoglobin 26, erythrocytes 792,000, leukocytes 4700, small lymphocytes 50, polymorphonuclears 50. On discharge his hemoglobin was 80, erythrocytes 4,032,000, leukocytes 4000, small lymphocytes 28, large lymphocytes 10, polymorphonuclears 48, eosinophiles 6, transitionals 7, myelocyte one.

The treatment consisted of Fowler's solution and sodium cacodylate. In December of the same year he came under our observation at Mercy Hospital. He was once more in poor condition and died there a few days after an injection of neodiarsenol.

R. M., aged thirty-six years, was admitted to the hospital September 15, 1915, and discharged December 27, 1915. On admission his blood showed hemoglobin 15, erythrocytes 496,000, leukocytes 4100, small lymphocytes 56, large lymphocytes 2, polymorphonuclears 38, eosinophiles 2, one transitional and one myelocyte. All pathologic forms of erythrocytes were present. At discharge his hemoglobin was 60, erythrocytes 4,120,000, leukocytes 8000, small lymphocytes 12, large lymphocytes 3, polymorphonuclears 82, a few poikilocytes. The treatment consisted of dilute hydrochloric acid, sodium cacodylate, Fowler's solution and normal saline flushings, 1 gallon every other day. He was readmitted to the hospital the following summer and his fortune was not so good. He died in September. The autopsy report dated September 23, 1916, reads: "Lemon-yellow discoloration of the subcutaneous fatty tissues of the body; edema of the pannicular adiposis and the mediastinal fatty tissues and of the renal fatty capsules; marked systemic anemia; marked hyperplasia of the spleen; 'red' bone-marrow; marked fatty changes in the myocardium, liver and kidneys; dilatation of the mitral and tricuspid rings; fatty changes in the intima of the coat of the aorta; passive hyperemia of lungs and liver."

In estimating the results of treatment such experiences as these are of great value. In a disease characterized by remissions such as have just been described it is easy to be oversanguine about the results of any treatment which may be employed.

In the group of 26 cases characterized by the predominance of nervous symptoms there were 19 males and 7 females. Only one patient was under forty; evidently the spinal-cord lesions are more liable to occur in older patients. The usual development of the symptoms might be summarized as follows: After a period during which the patient suffered from various disturbances of sensation, with or without a weakness of the legs, out of proportion to the general symptoms, incoördination or ataxia would supervene. Five of the 26 cases had urinary incontinence and 4 more had both urinary and rectal loss of control. The paralysis of the lower extremities was noted as flaccid 4 times; in 5 cases there was a spastic paralysis. The ocular reflexes were normal 22 times; in 2 cases there were Argyll-Robertson pupils; in another the pupils were noted as sluggish; in the other the right pupil was irregular and did not react to light. The patellars were absent 12 times and exaggerated 9. There was a Babinski in 12 cases. An ankle-clonus was seen 3 times. In 3 cases all the reflexes, biceps, triceps, patellar and Achilles were exaggerated. The abdominal reflexes were absent 5 times. There was one case of impotence; one of an aggravated

psychosis. In general the symptoms and physical findings pointed to a combined sclerosis; no case of true posterior sclerosis was seen. Among the 26 cases there were 14 deaths in the hospital. Only 3 of the 26 cases showed erythrocyte counts of less than 1,000,000 on admission; the leukocytes averaged 6630; there were only 4 cases with a lymphocytosis; in these the highest total leukocyte count was 4000.

We may infer that the predominance of the nervous symptoms renders the prognosis worse independently of the grade of the anemia. In 15 cases the blood Wassermann was negative; in 11 both blood and spinal fluid Wassermans were negative. In 1 case there was a positive blood Wassermann with a negative spinal fluid. The spinal fluid was negative, except for a slight increase of pressure once, in all the 12 cases. The process in the cord must be a selective toxic degenerative process, not inflammatory and probably not syphilitic. The symptoms and signs of cord involvement without a positive spinal fluid call for a careful examination of the blood.

Of the 22 cases which went to autopsy 5 proved not to be pernicious anemia. These included (1) a case of Laennec's cirrhosis in which the clinical diagnosis had evidently been based on the blood findings in spite of the ascites. The blood findings were in the main those usually regarded as characteristic of primary anemia, namely, hemoglobin 26, erythrocytes 1,165,000, color-index 1.3. There were also nucleated reds of all sizes. The leukocyte count was 11,200 and the differential normal. (2) Aortic stenosis and regurgitation, with a question about pernicious anemia because of the blood findings. These were hemoglobin 26, erythrocytes 1,340,000, color-index 1, leukocytes 3750. Differential count showed a slight polymorphonuclear relative increase. The autopsy showed the aortic lesions and a moderate interstitial nephritis. The characteristic findings of pernicious anemia were not present. (3) A case of streptococcic septicemia. A poor history had been obtained from this patient. The hemoglobin was 42, erythrocytes 1,916,000, color-index 1+, leukocytes 2850; nucleated reds were not recorded. The autopsy showed an acute serofibrinous pericarditis, embolic abscesses of the bowel and a "large septic spleen." (4) This patient gave a history of sudden onset two weeks previous to admission; there was fever, with chills, sweats, weakness, dizziness and nervousness. The ophthalmoscope showed small flame-shaped hemorrhages; there were inconstant rales in the left axilla about the sixth interspace. Gastric analysis showed no free HCl; total acidity 15. The feces were negative for pus, ova, parasites or blood. Blood examination showed hemoglobin 21, erythrocytes 1,208,000, color-index 1, leukocytes 4450, small lymphocytes 57, large lymphocytes 23, polymorphonuclears 13, basophils 1, myelocytes 6 and many nucleated reds. This case is particularly interesting because it simulates so closely the findings of an aplastic anemia. The onset described in

the history is somewhat inconsistent with pernicious anemia, but it is often difficult to get an accurate history from patients at the County Hospital. Aside from this the features which made the case one not to be regarded as typical of an essential anemia were the color-index just about normal and the predominance of lymphocytes, even though blood formation was still active, as shown by the presence of myelocytes and nucleated reds. Yet the blood findings in the absence of definite findings of another disease, the retinal hemorrhages, and the achylia made the diagnosis of pernicious anemia a logical one, and the result emphasizes what is perhaps the thing most to be remembered about pernicious anemia: the disease can be exactly simulated by the anemia dependent on some definite etiologic factor, such as carcinoma or tuberculosis. In this case the autopsy showed; "Nodular fibrocaceous tuberculosis of the tracheal, bronchial, biliary, retroperitoneal and mesenteric lymph nodes; bilateral fibrocaceous and nodular pulmonary tuberculosis; nodular tuberculosis of the kidneys, liver and spleen, multiple hemorrhages into the epicardium and lining of the stomach; moderate bilateral serosanguineous pleuritis." (5) This case presented the symptoms of weakness, fainting and edema of the feet, palpitation and loss of weight and pain in the back in the lumbar region of both sides. There were no gastric disturbances. The patient was fifty-two years old. There was dilatation of the heart. The liver was palpable. Reflexes and sensation were normal, although the "gait was uncertain." Spinal fluid was negative. Wassermann was negative on the blood and spinal fluid. Blood-pressure was 120 systolic and 70 diastolic. Urine was negative. Blood examination showed hemoglobin 35, erythrocytes 1,770,000, color-index 1.4, leukocytes 12,400. There is a note on the history: "The findings make quite certain the diagnosis of pernicious anemia." The feces were not examined. The autopsy disclosed an "annular carcinoma of the ascending colon." The pathologic conditions characteristic of pernicious anemia were not present. The pain in the back should not have been ignored and it may be emphasized that the leukocytosis should not have been disregarded.

Of the remaining 17 cases 9 went to autopsy as pernicious anemia alone. This diagnosis was confirmed in all without essential modification. In one case an acute pericarditis was found, probably terminal. In another the patient had evidently died of an acute pulmonary edema. The protocol of G. F., who died at the age of twenty-two years, may be taken as representative of the group: "Systemic anemia; marked fatty changes in liver, myocardium and kidneys; fatty degeneration of the lining of the aorta; 'red' bone-marrow; anasarca; passive hyperemia and edema of the lungs; moderate hyperplasia of the spleen; atrophic gastritis; left-sided fibrous pleuritis; disseminated petechial hemorrhages in the gastric mucosa and the mucous membrane of the urinary bladder." Two

cases were diagnosed pernicious anemia and lobar pneumonia; one pernicious anemia and chronic nephritis; one pernicious anemia and parotitis; all of these were essentially confirmed; 2 cases were both diagnosed pernicious anemia and organic heart disease. In both the diagnosis of pernicious anemia was correct; in 1 there was a chronic parenchymatous (large white) kidney but no heart disease other than the "marked fatty changes in the myocardium;" in the other the only cardiac changes noted were "dilatation of the mitral ring" and "fatty changes in the myocardium."

In 10 of the 15 cases the red count was below 1,000,000 on admission; two of the counts were below 500,000; the highest count was 2,000,000. The color-index was over 1 in all of the 15. The highest leukocyte count was 10,000 and the lowest 1300; the average was 4530. Seven, or 58 per cent. of the cases in which a differential leukocyte count was made showed a relative lymphocytosis. In one case the total count was 4900, with a lymphocyte count of 88 per cent. In 12 of the 15 cases nucleated reds were found. Our views of the blood findings, commonly accepted as characteristic of pernicious anemia, were confirmed by these autopsies; the cases which went to autopsy, in which the pathology of pernicious anemia was found, had conformed clinically most closely to the accepted standards of pernicious anemia. Of the 15 patients 12 were men; 2 were under thirty years of age (one was only twenty-two), 6 between thirty and forty, 5 between fifty and sixty and 2 over sixty. All were white.

An apical systolic murmur was found in 3 cases, basal systolic in 4 and a murmur systolic in time, both at base and apex, in 2. In 1 case there were described a presystolic thrill and murmur at the apex; no valvular disease was found at autopsy. In another case the history contained a record of a presystolic thrill at the apex, a presystolic murmur at the apex and systolic and diastolic murmurs at the base. Duroziez's phenomenon was also present. *The autopsy protocol stated that the cardiac valves were normal.* The maximum systolic blood-pressure was 138 and the minimum 90; of 11 readings the systolic pressure was below 115 in 8; the average pulse-pressure was 50. The spleen was palpable in 5 cases. The urinary findings also corresponded to those obtained in the cases observed only clinically; the specific gravity was low in 10 cases; otherwise the findings in these were negative; in 1 there was a trace of albumin; in 1, without albumin, a few finely granular casts; in 2 without albumin, a few hyaline casts. Only 1, the case diagnosed as pernicious anemia and nephritis, showed albumin and hyaline and granular casts. The patient, in whom the chronic parenchymatous nephritis was later found, had shown nothing in her urine except some finely granular casts. The blood-pressure in this case was not taken. In the autopsy reports atrophy of the gastric mucosa was mentioned only 3 times. The spleen was hyperplastic in 10 cases.



Two cases went to autopsy with a diagnosis of "suspected abdominal malignancy;" in 1 case the color-index was high; the highest leukocyte count was 6800; there were no nucleated erythrocytes; in the other case no blood counts were recorded, as the case apparently was regarded as certainly one of malignancy. In both cases the characteristic findings of pernicious anemia were present.

Fifteen cases in another group were discharged as pernicious anemia but with some qualification. Of these 10 were males; the youngest patient was ten; 4 others were under thirty; 5 between thirty and forty and 5 over forty. There is a notable variation here from the age incidence in the cases of true pernicious anemia. In the latter the proportion of patients over 40 was distinctly greater. Six of the 15 patients died in the hospital.

This group can best be considered in several subgroups:

Two cases of pernicious anemia with nephritis. In one case the urine contained much albumin, hyaline and granular casts and red blood cells; in the other there was generalized edema, with dyspnea, headache and insomnia; the color was waxy; there was evidence of fluid in both pleural cavities; the urine was albuminous, containing hyaline and granular casts. The respective blood counts were hemoglobin 36, erythrocytes 1,690,000, color-index 1.4, leukocytes 6400, differential count normal; no nucleated reds. Hemoglobin 15, erythrocytes 1,560,000, color-index, 0.4, leukocytes 26,200. Obviously the latter may be dismissed as nephritis, with severe secondary anemia.

Three cases with hemorrhages: The first, a man aged thirty-seven years, had epistaxis and hemorrhages from the bowels; the gums bled easily; there were also hemorrhages from the ear. The blood count showed hemoglobin 22, erythrocytes 1,165,000, color-index about 1, leukocytes 12,000, with 86 per cent. polymorphonuclears. The history is that of a purpura hemorrhagica; the findings are those of a secondary anemia.

The second, a man, aged forty-five years, who complained of loss of blood during defecation, persisting for some time and growing worse, until at the time of entrance to the hospital he was passing an ounce or two with every movement of the bowels. No hemorrhoids were found. The blood count was hemoglobin 37, erythrocytes 1,808,000, color-index 1.1, leukocytes 3600, with a relative lymphocytosis, small lymphocytes 38 per cent. and large 15 per cent. There was poikilocytosis but no nucleated reds were found.

The third, a man, aged thirty-six years, with hemoptysis and severe nose-bleed. The day before his death it was noted that he had a "profuse hemorrhage from mouth and nose." The blood count shortly before his death was hemoglobin 25, erythrocytes 960,000, color-index 1.3, leukocytes 21,300; polymorphonuclears 84 per cent.; a few nucleated reds. Again the findings are not typical of pernicious anemia.

Four cases of pernicious anemia with heart disease. The first showed general anasarca and dyspnea, with marked evidence of ascites; there was a systolic blow at the apex, with a gallop rhythm. The blood count was hemoglobin 10, erythrocytes 742,000, color-index 0.7, leukocytes 4800, polymorphonuclears 75, myeloblast 1.

The second patient had mitral insufficiency with healed apical tuberculosis. The blood-count on admission was hemoglobin 18, erythrocytes 896,000, color-index 1.2, leukocytes 2550; there was a relative lymphocytosis, these cells making 50 per cent. After transfusions the patient improved very much, leaving the hospital ten weeks after admission with a red count of 2,608,000 and a hemoglobin of 45. The dilated heart, the mitral murmur and the evidence of old tuberculosis fail to convince one that this was not a case of pernicious anemia, with cardiac findings, such as have been discussed. There was, moreover, no record of generalized edema nor of cardiac dyspnea.

The third was a case diagnosed as pernicious anemia, with mitral stenosis, regurgitation and aortitis. There was a history of rheumatism and symptoms of cardiac incompetency for eighteen months. There were moist rales over the bases of the lungs. Blood count was hemoglobin 17, erythrocytes 1,244,000, color-index 0.8, leukocytes 6800, polymorphonuclears 77 per cent.; no nucleated reds.

The fourth case was characterized by generalized anasarca, dyspnea and a tendency to nose-bleed; the heart was very irregular. The blood count was hemoglobin 23, erythrocytes 719,000, leukocytes 8000, color-index, 1.6, differential normal; very few nucleated reds. The urine was negative. The feces contained no blood, but did show a great many of the parasites known as *trichomonas intestinalis*, an organism usually regarded as non-pathogenic.

Two cases with a definite focus of infection. The first is one of the most interesting cases of the series. The patient, a man, aged fifty-four years, entered the hospital May 6, 1918. He presented the usual symptoms of pernicious anemia, but in addition complained of a pain in the left leg, deep in the bone, which had been present for six years. The blood count on admission showed hemoglobin 45, erythrocytes 1,190,000, color-index 1.9, leukocytes 3200, poikilocytosis and small lymphocytes 78 per cent., large lymphocytes 6 per cent., polymorphonuclears 14 per cent., eosinophils 2 per cent., 1 normoblast was found. Four weeks later his erythrocytes were 770,000. He was transfused June 30, 600 c.c. of blood being given. On July 15, his blood count was hemoglobin 29, erythrocytes 1,370,000, color-index 1.08, leukocytes 6650. One week later an incision was made over the upper one-third of the left tibia through the periosteum and 4 ounces of pus were discharged. Eight days after the operation the hemoglobin was 45, erythrocytes 2,220,000, color-index 1.03, leukocytes 7750. Two weeks after the transfusion his hemoglobin had increased from 18 to 29, his erythrocytes from

770,000 to 1,370,000; eight days after the successful drainage of a subperiosteal abscess the hemoglobin had increased from 29 to 45 and the erythrocytes from 1,370,000 to 2,220,000. He was discharged September 9 with a hemoglobin of 63, erythrocytes 3,280,000 a color-index of 1 and a leukocyte count of 6300.

The second was the case of a boy, aged seventeen years, who had been operated on for an osteomyelitis of the left femur ten months previously. For a while he ran a temperature of 104°. Chronic osteomyelitis was found on Roentgen-ray examination but no local symptoms appeared and no operation was done. No other focus of infection was found. His blood count was hemoglobin 27, erythrocytes 725,000, color-index 1.92, leukocytes 2900, small lymphocytes 44 per cent., large lymphocytes 10 per cent., polymorphonuclears 44 per cent., eosinophils 1 per cent., transitionals 2 per cent. This patient died after a transfusion.

The question of diagnosis in this instance must be regarded as unsettled.

Of the 4 cases remaining one was probably a case of sprue and so noted. He had been a patient in a U. S. Army hospital in the Philippines. For two years he had suffered with stomatitis and diarrhea. The stools were frothy, whitish, very foul and contained no blood. The blood count, at the lowest, showed hemoglobin 20, erythrocytes 990,000, leukocytes 4000; no nucleated reds and a normal differential white count.

The second was the case of a man in whom the Roentgen ray discovered a lesion at the pylorus. The blood examination showed the findings usual in secondary anemia except for a high color index and a white count of only 5400, once as low as 2800.

The third case was one of "old pulmonary fibrosis, with an advanced secondary anemia" (a red corpuscle count of 1,480,000) and a high color-index.

The fourth was a case originally diagnosed as Banti's disease and discharged from the hospital October 26, 1915, with that diagnosis. She returned in December of the same year and died two months later of pneumonia. She entered the hospital the first time, with a marked ascites. A large spleen was palpated and the patient stated that she had known of this enlargement for twenty years. She was tapped three times. The specific gravity of the fluid was 1006 to 1010. Her lowest blood count was hemoglobin 25, erythrocytes 3,000,000, color-index, 0.5, leukocytes 3400. At the time of the second admission the blood examination showed hemoglobin 5, erythrocytes 870,000, leukocytes 34,000, polymorphonuclears 87 per cent.; all forms of nucleated reds. The most plausible theory about this case is that some of the findings of pernicious anemia (particularly the presence of nucleated erythrocytes) had developed on the basis of a long-standing secondary anemia. The original diagnosis of Banti's disease was probably correct.

In summarizing the last group of cases we find that in only 2 cases was the spleen palpable. One of these cases was the one originally diagnosed as Banti's disease; in 10 cases it was expressly stated that the spleen was not palpable. In 9 cases the color-index was above 1. There was a leukocytosis of more than 10,000 in 3 cases. In no case were the nucleated forms of the red corpuscles easily found. In 8 cases none were found and in the others they were very rare. In only 3 of the cases, or 20 per cent., did the lymphocytes exceed the polymorphonuclears. In the cases demonstrated at autopsy as pernicious anemia 43.7 per cent. showed relative lymphocytosis. In 2 of these 3 cases there were no nucleated reds; the third was the case of suppurative periostitis already described, which showed a high index, a relative lymphocytosis and very few normoblasts. As a general conclusion we may say that these findings warrant the opinion that great reserve should be exercised about making a diagnosis of pernicious anemia when all the characteristic blood findings are not present. In this type of case search for a definite etiologic factor is most urgent.

It would be a thankless task to attempt a review of the medicinal therapy, but we are interested in the use of human blood as a therapeutic procedure. There were in all records of 30 injections of human blood in 19 cases; 26 of these were intravenous transfusions with citrated blood in 16 patients; 3 were subcutaneous injections of whole blood, in 2 patients, and there was one subcutaneous injection of defibrinated blood.

In the last case 200 c.c. of defibrinated blood were injected subcutaneously, without reaction or result. In two cases whole blood was used subcutaneously. In one 20 c.c. of whole blood were injected without reaction or result. In the second one injection of 30 c.c. was given, with a slight reaction and no therapeutic effect. Four days later a second injection of 60 c.c. was given. Three hours after the injection the patient had a chill lasting twenty minutes: the condition improved but the pulse remained rapid and weak. Four days after the injection the temperature went to 102.6°. The next day evidence of suppuration was discovered in the buttock into which the injection had been made. Four days later the patient died. Death is attributable to the injection of blood only indirectly; it was not the result of a reaction but of an infection which the already debilitated patient could not stand.

Twenty-six intravenous injections of blood with sodium citrate were given to 16 patients; 2 of these were of small amounts, 10 c.c. to each of two patients. There was no reaction in either case and no benefit was apparent. The other transfusions varied in amount from 200 to 600 c.c. Three of these were done at Wesley Hospital on a patient afterward admitted to the County. In 4 of these no improvement is noted on the chart; after 17 of the transfusions distinct improvement was noted. We may cite 3 cases: the first,

with a hemoglobin of 16 and a red count of 888,000, was transfused the first time September 24, 1916; three days later the blood examination showed hemoglobin 16, erythrocytes 1,536,000. The count fell to 808,000 on October 2; on October 3, another transfusion was done; on October 4, the count was 1,840,000; each transfusion was followed by an increased leukocyte count; following the second transfusion improvement was steady and the patient, much better, was discharged November 21.

In the second case the red count, August 5, 1918, was 1,050,000, with a hemoglobin of 30 and a leukocyte count of 2050. Transfusion was done on the seventh, and nine days later the blood examination showed hemoglobin 50, erythrocytes 4,070,000, leukocytes 4100. The patient, in good condition, left the hospital September 9.

A third case after the first transfusion showed a rise in the erythrocytes from 990,000 to 1,300,000; after the second, the hemoglobin rose from 25 to 35, the erythrocytes from 990,000 to 1,300,000; after the third the hemoglobin was unchanged at 30; the erythrocytes rose from 1,700,000 to 2,350,000. This patient did not continue to do well. A splenectomy was advised but refused; the patient shortly afterward was taken home in poor condition against our advice. There were 11 patients in this group showing improvement after transfusion; prior to the first transfusion the highest erythrocyte count was 1,200,000; only 3 patients had more than 1,000,000 erythrocytes; 8 of the 11 left the hospital improved (one improved after the transfusion, but much more rapidly after a collection of pus was evacuated, as mentioned elsewhere), 1 left the hospital in poor condition and 2 died in the hospital; one of these latter, shortly before her death, had an erythrocyte count of 3,800,000 and a hemoglobin percentage of 75; it had not been deemed necessary to transfuse her for four months; she died of complications incident to combined cord degeneration. We may say that of the 11 cases 9 showed marked improvement in the blood condition.

Three deaths occurred shortly after transfusion; in one case the transfusion was carried out as a measure of last resort in a moribund patient; there was no typical reaction and the death cannot be charged to the transfusion. In 1 case while the transfusion was in progress the patient complained of "dizziness and faintness, then became dyspneic, was nauseated and tried to vomit; there was headache and a clammy perspiration broke out; the transfusion was stopped. One-half hour later a severe chill occurred, lasting fifteen minutes; two hours later an attack of severe abdominal pain, dyspnea, pulse imperceptible; death occurred one-half hour later." The other fatal reaction took practically the same course. There were in all six severe reactions and three mild ones; seven of the transfusions were followed by no reaction.

There is a record of one splenectomy in the series; the operation was done after the patient had been in the hospital for three months

and had made a notable gain; the patient was discharged in good condition one month after operation.

In reviewing the results of this study, we find:

1. The clinical complex known as pernicious anemia presents certain characteristic blood findings, particularly the high color-index, the presence of many large erythrocytes and of nucleated red cells, especially megaloblasts, and a tendency to a leukopenia, with a relative lymphocytosis; the clinical symptoms, though secondary in importance from the standpoint of diagnosis, are yet distinct and definite. The progressive weakness, the gastric disturbances; the dyspnea, pallor, the cardiac findings and the edema of the feet are the most typical and constant findings.

2. Though pernicious anemia has its own characteristic diagnostic findings these may be simulated closely by anemias resulting from various diseases; in fact, the blood picture of pernicious anemia may be presented exactly as the result of some definite septic, toxic or malignant condition. The diagnosis should rest not on the blood findings alone nor on the blood findings and symptomatology, but on these two features in the absence of any discoverable cause for the anemia.

3. The disease is more common in males and is most frequent in the fourth and fifth decades of life.

4. The cardiac symptoms and physical findings (the murmurs and the dilatation of the heart) are so constant as to be looked upon as among the most common symptoms of the disease. Anatomically valvular disease is not a part of pernicious anemia; the cardiac findings are the result of myocardial weakness and relative insufficiency. Ascites and anasarca are not symptoms of pernicious anemia though there is a possibility that they may result from cardiac incompetency, this event is so unusual that their presence demands explanation.

5. The systolic blood-pressure is almost never above normal but tends to be below the lower limit of normal; the diastolic pressure is disproportionately low and the pulse-pressure high.

6. The urine is usually of a fairly low specific gravity, rather increased in quantity, and rarely contains albumin. The presence of albumin is not to be accepted as a usual finding in pernicious anemia; its presence with casts means nephritis, which may be the cause of the anemia rather than the effect.

7. Pernicious anemia is characterized by an irregular temperature, which is not often above  $101^{\circ}$ ; there are often recessions to normal of variable duration.

8. Achylia gastrica is so much the rule that the presence of free HCl may justifiably raise a doubt as to the diagnosis.

9. The Wassermann reaction occurs infrequently in pernicious anemia. In 46 cases there was a percentage incidence of 6.5; the general run of cases in a large charity hospital would probably

show a higher percentage. It is possible that certain changes in the blood incident to the disease interfere with the reaction.

10. The gradual decrease in the leukocyte count, especially in the relative and absolute number of polymorphonuclears, is of serious prognostic import. The diagnosis of pernicious anemia should be made with the utmost reserve in the presence of a leukocytosis.

11. The negative spinal fluid tests in the presence of well-established cord disease point to a toxic degenerative process in the cord rather than an inflammatory process. Disease of the cord, with pernicious anemia, usually means an involvement of the lateral and posterior columns, a combined cord lesion. The presence of evidences of cord disease is of unfavorable prognostic import; the prognosis in these cases is grave, out of proportion to the blood findings as compared to the cases not so complicated. These patients are less likely to live long enough to develop advanced grades of anemia.

12. Transfusion of blood will not cure but will often prolong the patient's life. The severe reactions which occurred in this series were likely the result of imperfect technic; the procedure has really been developed from its inception in the years covered by this study; transfusions are now being done with a much lower percentage of reaction. Yet the experiences noted here may have a valuable lesson for us. The transfusion of citrated blood is a simple procedure but not a harmless one. Before the operation is undertaken the bloods of donor and patient must be demonstrated to be compatible by an acceptable and approved technic.

## REVIEWS

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A MANUAL OF PHYSICAL DIAGNOSIS. By AUSTIN FLINT, M.D., LL.D. Eighth edition, revised by HENRY C. THACHER, M.S., M.D., Assistant Professor of Clinical Medicine in the College of Physicians and Surgeons of Columbia University, etc. Pp. 362; 26 illustrations. Philadelphia and New York: Lea & Febiger, 1920.

As the pendulum swings back toward the greater importance of the simpler methods of clinical study, we may expect more and more attention to be focussed on the fundamental physical examination of the patient. Perhaps no one in this country has contributed more to the underlying principles involved in this branch of clinical medicine than Austin Flint. It is therefore a pleasure to have his simple and pointed presentation of the subject kept thoroughly up to date, brought to our attention from time to time as the new editions arrive. The present revision by Dr. Thacher includes some new material, especially upon effort syndrome, the unusual signs that may sometimes be heard over the normal heart and the diagnosis of pulmonary tuberculosis on uncertain and insufficient evidence; yet the *Manual* retains the simple and logical presentation of the original author. Although the first third of the book is given over to a discussion of percussion and auscultation in health and disease the other methods of examination, particularly inspection and palpation, are not neglected when the actual physical diagnosis of disease is under consideration. In each instance the physical conditions met with in health are presented before those alterations met with in disease. Although too brief to cover the subject in great detail and to enter into controversial matters, this *Manual* will continue to rank as one of the standard works on physical diagnosis.

T. G. M.

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WHEELER'S HANDBOOK OF MEDICINE. By WILLIAM R. JACK, B.Sc., M.D., F.R.F.P.S.G. Physician to the Glasgow Royal Infirmary; Lecturer in Clinical Medicine in the University, Glasgow. Sixth edition. Pp. 561; 28 illustrations. Edinburgh: E. & S. Livingston; New York: William Wood & Co., 1920.

This small handbook, which, though containing more than 500 pages, is small in length and width, apparently presents the impor-



tant facts of internal medicine in a brief and precise manner. The book is a good example of the small manuals of medicine, but has the usual faults characteristic of such medical abstracts. The only obvious advantage of these abridged editions seems to be in the marshalling of the salient facts of medicine so that one reviewing for examinations may cover the entire subject in a short time.

J. H. M., JR.

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THE MEDICAL CLINICS OF NORTH AMERICA. Volume III, Number 6. Pp. 1493-1779. Philadelphia and London: W. B. Saunders Company, 1920.

THE Chicago number of the *Clinics of North America* contains a large number of case reports and articles on various types of diseases considered for the most part from a diagnostic and therapeutic standpoint. Dr. Mix contributes an article on encephalitis and also one on mediastinal tumors. Dr. Abt writes on infantile eczema as well as presenting a symposium clinic. Dr. Williamson discusses lymphosarcoma of the neck and pernicious anemia, with extreme dropsy, while Dr. Strouse deals with urticaria and angio-neurotic edema. Dr. Carr reports 2 cases—1 of bronchiectasis with pulmonary hemorrhage and 1 of gall-stones with chronic jaundice. Colic in the breast-fed infant is the subject selected by Dr. Grulee, while Dr. Bassoe describes some cases of brain abscess. Dr. Sonnenschein introduces the subject of headache from the point of view of the otolaryngologist. Cerebrospinal syphilis and encephalitis are gone into carefully by Dr. Hamill, while Dr. Hamburger demonstrates the protean character of angina pectoris. Dr. Friedman writes on gastric ulcer and chronic enterocolitis. The remaining three articles are by Dr. Hess, Dr. Wright and Dr. Portis. A particularly suggestive contribution is that of Dr. Byfield, who analyzes some of the more important causes of error in diagnosis and shows us the mistakes that we make are frequently due to carelessness, lack of complete examination and improper history-taking, errors which we can successfully overcome by proper care and study of the patient.

J. H. M., JR.

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SIMPLIFIED INFANT-FEEDING. By ROGER H. DENNETT, M.D., Associate Professor of Diseases of Children, New York Post-Graduate Medical School, etc. Second edition. Pp. 385; 14 illustrations. Philadelphia and London: J. B. Lippincott Co., 1920.

THIS book is a departure from the usual in infant-feeding. There is no review of the literature. The author describes a method of

feeding based upon the calorific requirements of the infant. It is hardly necessary to enumerate the various chapters, but the principles followed may be shown by quoting this much: "In prescribing food for any infant there are three main points for consideration: (1) It should contain the proper elements to maintain nutrition and allow growth; (2) it should be digestible; and (3) it should contain the proper quantity of food, which is best estimated by caloric standards."

Certainly one must have some rule or system by which to judge the requirements of a normal infant—always realizing that the infant is an individual and may be subject to variation. From the basis of the normal requirement, the food of the sick infant is to be manipulated as indicated. By following Dr. Dennett's method one can be quite successful in infant-feeding. However, the reviewer feels that it is not a complete method and one should also be cognizant of the percentages of the various ingredients, and their actual amount, present in the mixture. It is the custom of many to use the calories of a food as the check upon the method, rather than as the actual basis upon which to calculate requirements.

A. G. M.

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THE CATARRHAL AND SUPPURATIVE DISEASES OF THE ACCESSORY SINUSES OF THE NOSE. By ROSS HALL SKILLERN, M.D., Professor of Laryngology, Graduate School of Medicine, University of Pennsylvania, etc. Third edition, thoroughly revised and enlarged. Pp. 418; 300 illustrations. Philadelphia: J. B. Lippincott Company, 1920.

SPACE does not permit, nor is it necessary to attempt, an extended review of Skillern's well-known *Accessory Sinuses*, now in its third edition. The early exhaustion of the two previous editions demonstrates the necessity for and popularity of the work, and it is the recognized authority on the special subjects to which it is devoted. The new edition contains all the material and information of the former editions, and in much the same form, additions having been made when called for, due to progress in this special field, and bringing the subject-matter up to date by many references to the literature of the last four years. The author has, moreover, incorporated into the text the observations of himself and others on infections and injuries of the sinuses during the recent war, in so far as they apply to civilian practice.

Particular attention has been given to the question of sinusitis in infants and children, on which much work has been done in the last few years by Skillern, Dean and Armstrong, Coffin, Oppenheimer and others. This is an important subdivision of the subject, much neglected by the profession until comparatively recently, and one

that is of peculiar interest not only to every rhinologist but to the pediatricist and general practitioner as well. As the subject is still in the developmental and theoretical stage, undue space is not given to it, the accepted facts, as far as demonstrated, being alone presented.

"When to operate in maxillary sinusitis" is an entirely new contribution, introduced with the idea of clearing up, in a systematic way, many of the difficulties encountered by beginners in the specialty. The subject is thoroughly discussed from all angles and plain rules for guidance given.

New methods discussed and described in detail are Lothrop's operation on the frontal sinus and Sluder's upon the ethmoid labyrinth. The chapter upon the sphenoid sinus has been entirely and thoroughly revised. Many new illustrations have been added describing these and other procedures, so that the volume remains, as it has always been, one of the best and most clearly illustrated text-books in medicine. In view of the fact that since their return from military service many recruits have been and are being made to the specialty of rhinology, this work should continue the popularity of the previous editions, and be an acceptable text-book in the numerous institutions now giving postgraduate instruction in this subject.

G. M. C.

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THE DON QUIXOTE OF PSYCHIATRY. By VICTOR ROBINSON. Pp. 334. New York: Historico Medical Press.

THIS book gives a friendly account of the life of Dr. S. V. Clevenger, a distinguished psychiatrist, who was one of the early leaders in the institution treatment of the insane in this country. It is a very interesting book, for it not only discusses Dr. Clevenger, but gives interesting side-lights of other figures in medicine of men who were contemporaries of Clevenger, such as Leidy, Pepper and Hammond. It is a worthy tribute to a man who has meant a great deal in psychiatry.

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MANUAL OF PRACTICAL ANATOMY-(CUNNINGHAM). Revised and edited by ARTHUR ROBINSON, Professor of Anatomy in the University of Edinburgh. Seventh edition. Volume II. Pp. 524; 23 illustrations. New York: William Wood & Company, 1920.

IN this edition the general text has been revised and many new figures, representing dissections, sections and radiographs have been added. Instructions for dissection have been printed in a distinctive indented type, a feature of the book that will especially

appeal to the student. As a result of the additions to the work it has been thought advisable to publish the book in three volumes. Thus the second volume considers the thorax and abdomen.

The text matter is nicely arranged and the writer's style makes it very easy reading.

The new nomenclature is used throughout but in all instances the older terminology follows in brackets.

The manual is of a convenient size, printed with a clean clear-cut type and on a nice grade paper.

It makes a most excellent and convenient reference work.

E. L. E.

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MANUAL OF PSYCHIATRY. By AARON J. ROSANOFF, M.D. Fifth edition. New York: John Wiley & Sons, Inc., 1920.

THIS fifth edition is an outgrowth of the English translation of the French *Manuel de Psychiatrie*, by J. Rogues de Fursac. In addition to the author the contributors are: H. L. Hollingsworth, associate professor of psychology, Columbia University, who contributed some chapters on psychology; Miss Mary C. Jarrett, who contributed the chapter dealing with applications of sociology in psychiatry; Clarence A. Neymann, M.D., who discusses lumbar puncture, cell count and chemical tests of cerebrospinal fluid. The book is divided into three parts: First, dealing with general psychiatry; second, special psychiatry; third, appendices, dealing with the technic of diagnostic procedures.

The first part, which deals with general psychiatry, is first rate, for here the author deals with a subject with which he is thoroughly familiar—that is psychiatry and its treatment. Perhaps those who are familiar with Freudian methods might consider the chapter on psycho-analysis as inadequate.

The second part, dealing with special psychiatry, is also well done, with the exception of that part which deals with psychoneuroses. The author bases his views entirely upon his army experience, and particularly that obtained in Plattsburg. He comes to the conclusion that hysteria and malingering are one and the same thing. He further states that "it seems therefore justifiable to conclude that an illicit motive is an essential part of the mental mechanism of hysteria; but such motive need not be of a sexual nature, although it undoubtedly very often is." In discussing the hysteric personality, he states that the essential feature consists in a character defect which places the hysteric individual in close relation to the criminal.

The average neurologist will entirely disagree with the viewpoint quoted in the above paragraph, for it is held by one trained altogether in psychiatry, and furthermore based on the very limited experience

chiefly obtained, as admitted by the author, from a few months' experience among psychoneurotics in Plattsburg.

Part three deals with the technic of special diagnostic procedures, two of the chapters being written by Dr. Neymann. These deal with lumbar puncture and chemical tests, such as the Wassermann. They are not sufficiently technical for a laboratory worker but give the reader an idea as to what these processes consist of. The Stanford revision of the Binet-Simon intelligence scale takes up a whole chapter of seventy pages. A chapter consisting of seventy-four pages concerns itself with the Kent-Rosanoff free association test. These in their length are out of all proportion to the rest of the book, for dementia precox is given only thirty-two pages.

With these exceptions the book is a good one and the reader will find whatever advice he is looking for presented in a very sane, normal fashion.

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SURGICAL CLINICS OF CHICAGO. August, 1920, Number. Vol. IV, No. 4. Pp. 214; 80 illustrations. Philadelphia: W. B. Saunders Company, 1920.

THE high standard of this work is still maintained in this number. It contains seventeen original articles by members of the contributing staff from the various Chicago hospitals. As the writers continue from number to number they more and more present their subjects as the general medical reader needs them presented. Yet they at the same time give minutiae and detail that appeals to the special reader.

The work fills a need and fills it well.

E. L. E.

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THE NARCOTIC DRUG PROBLEM. By ERNEST S. BISHOP, M.D., Pp. 136. New York: The Macmillan Company, 1920.

THE author believes that drug-addicts suffer from a disease and that the victims should not be spoken of as "drug fiends" or the users as having the "drug habit." He thinks if addicts are carefully handled, first getting them in excellent physical condition and then withdrawing the opiates in a manner not harmful to the patients, that they can be cured of being addicts.

Dr. Bishop is of the opinion that the reason opiates are used is because of bodily need and not for the enjoyment that is received from their use. He further states that too many people think of these persons as being morally weak, unable and unwilling to discontinue the use of narcotics, whereas to do so causes physical

suffering. According to the author many of the legislators, administrators and even physicians do not fully understand the situation, and when the Harrison law was passed making it impossible for drug addicts to obtain narcotics, this either drives them into the "under-world," or, if unable to obtain opiates through illegal methods, to escape physical suffering they resort to suicide.

The book is written in a very clear manner; in fact, the author impresses upon the reader too often the same facts and few new thoughts are introduced after the first few pages. Besides the repetition the author strays from the point at issue, and in discussing any particular phase he invariably reverts to some part of the question previously discussed at length.

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THE DIAGNOSIS OF NERVOUS DISEASES. By SIR JAMES PURVES STEWART, K.C.M.G., C.B.M.D. (Edin.), F.R.C.P. Fifth edition. Pp. 557. New York: E. B. Treat & Co., 1920.

THIS is the fifth edition of Stewart's well-known *Diagnosis of Nervous Diseases*. The fourth edition was written three years ago, while the author was on war duty in Saloniki. The present edition has been revised and in part rewritten. A short chapter on war neuroses regarded from their clinical standpoint has been added.

The scheme of the book is well worked out. It is not intended by any means to be an exhaustive text-book, but, as the title indicates, it is a diagnosis. The anatomy and physiology are adequately and well done. Aphasia is treated from the old and well-known standpoint and the recent controversial phases are omitted. Cerebellar conditions are adequately discussed, with the exception that no attention is paid to the more recent studies of localization. Peripheral nerve conditions are exceedingly well done, and so far as the reviewer knows this is the only book on neurology which has a chapter on organic war lesions. The fact that it has reached its fifth edition is ample evidence that the book is well worth while.

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CAST GOLD AND PORCELAIN INLAYS. By HERMAN E. S. CHAYES, D.D.S., New York. Pp. 382; 372 illustrations. St. Louis: C. V. Mosby Company.

THIS is a scholarly addition to dental literature reflecting thoroughness and minute care on the part of the author in every detail.

The introduction comprising some fifty pages on sequence of

thought and the value in teaching is a most finished, thoughtfully written expression of fundamental facts well worth reading, although rather mature for the average student and not closely allied to the general subject.

The chapter on cavity preparation is comprehensive and practical. There is nothing radical or new, but it reflects the best thought on the subject, fully illustrated and giving a clear idea.

The author has gone most fully into the subject of cast gold fillings, the failures caused by faulty impressions, how to obviate them, and a very full and fair description of different casting methods and the results obtained.

The method for inlay work, their treatment and casting, splinting of teeth and the restoration of occlusal balance, and the treatment of the indirect method has the full allotment of space it deserves.

Porcelain work is well described in detail and comprehensively, which applies to the entire work.

Twenty pages are devoted to light and color, followed by a chapter on ductless glands as expressed in the human mouth, endocrinodontia. This is a field dentists must become more familiar with, and although there are few of us that can agree with Dr. Kaplan that the "frequency of decay in lower molars as compared with anterior teeth is due to the position of the submaxillary glands, etc.", the idea is very progressive.

P. L. L.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

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**Immediate Closure of Empyemata.**—HATHAWAY (*British Med. Jour.*, May 29, 1920, p. 734) has always used a local anesthetic but is inclined to think that when handling the lung a little general anesthetic with it is useful. He resects sufficient rib, either a long section of one rib or adjacent parts of two ribs, to allow of the introduction of the whole hand into the pleural cavity. This is the most important point, because, after evacuation of the pus, it is essential to pass the hand into the chest cavity and strip off the collapsed lung all adherent fibrin and separate the lung from all adhesions. In any early case this is easily done, but an old standing one will require much freeing of the lung in order that it may recover its reëxpansibility. He then washes out the pleural cavity with flavine until the fluid comes away quite clean, and fills the chest with a 2 per cent. suspension of iodoform in sterilized paraffin. The pleural wound is then sewn up with catgut, not that he thinks this is very important, because these stitches soon give way. He then carried out immediate closure of the skin with deep sutures, so as to leave no "sucking" wound. When dressing on the next and following days the wound will be bulging. This is due to a mixture of pus and iodoform and paraffin being pushed out of the pleural cavity by the expanding lung under the skin. Daily he introduces the needle of an exploring syringe between the edges of the wound—this is quite painless—and extracts all the fluid he can. This process usually takes ten to fourteen days, depending upon the reëxpansion of the lung. Daily bacteriological report of this fluid shows that the number of organisms in a field steadily diminishes. A certain amount of this mixture of pus and iodoform and paraffin will ooze out also in the dressings. Harris has now sutured nine cases. His only failure was a tuberculous case. The patient died in twenty-four hours. Postmortem the lung was found tied in a knot at the root, he had evidently not explored the chest sufficiently with his hand. All of the other eight cases made good and rapid recoveries. The duration of the disease in these cases varied from two to six weeks, after the resolution of the primary pneumonia.



**Volvulus of the Cecum; Double Obstruction.**—SMITH (*British Med. Jour.*, February 28, 1920, p. 289) reports a case of volvulus of the cecum, the true nature of which was only discovered at autopsy. The patient, a male, aged thirty-three, had had attacks of indigestion for some years. They were not severe. He also had constipation, pain and discomfort after meals, with occasional vomiting. He had a sudden acute attack of abdominal pain, with vomiting. When seen by the author twenty hours later he had all the signs of symptoms of an acute abdominal catastrophe. The vomiting was not fecal. A right paramedian incision was made. The cecum and ascending colon were distended and turned toward the midline, forming a definite volvulus. The transverse colon was empty. It appeared that the hepatic flexure was the seat of the obstruction, so it was explored and an acute kink was found. A Paul tube was inserted into the cecum. Twenty-four hours later he developed symptoms of further obstruction, and in spite of treatment he died twenty-four hours later. Autopsy disclosed the following: From the point of obstruction at the hepatic flexure there stretched a thick, organized adhesion, passing across and adherent to the anterior leaf of the mesentery and fixed firmly to the ileum about two inches from the ileocecal valve. The small gut was acutely kinked here in a manner similar to that at the hepatic flexure. The original lesion was a tuberculous affection of the mesenteric glands. The author thinks the death due to the ileal obstruction and not to a paralytic distention.

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**The Uses of Free Transplants of the Fascia Lata in Surgery.**—TURNER (*British Med. Jour.*, January 17, 1920, p. 79) says that it is to the late Murphy of Chicago, that we owe the more general use of free transplants of the fascia lata; he used these extensively in arthroplasty. Turner has used it in arthroplasties, in protecting deeper structures, such as sutured nerves or tendons, during the slow healing of wounds by granulation or when the superficial tissues are so much damaged that their recovery after suture is likely to be attended by sloughing. It is also exceedingly useful for the replacement of lost tendons. They are also useful in covering the exposed brain where the membranes are ruptured. Turner has used free fascial transplants in repairing the urethra. The transplants behave exceedingly well even when infection occurs. All transplants are removed through a vertical incision on the outer side of the thigh, and except where the transplant has been a very small one no attempt is made at suture of the cut edges.

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**Mammary Sarcoma in Old Age.**—GRAVES (*British Med. Jour.*, January 17, 1920, p. 81) reports a case of a female, aged ninety-eight years, with sarcoma of the breast and pulmonary metastasis. The lesion was noticed three and a half months previously while the patient was being given a bath. The breast was not enlarged but was painful and several hard, small masses were scattered through the substance of the gland. The axillary lymphatics were not enlarged. Owing to senility operation was not undertaken. The breast rapidly increased in volume and soon attained the size of a foot-ball. The skin became eroded. Shortly before death the patient coughed up a small clot of blood. The microscopic sections showed a large spindle-celled sarcoma.

**Subcutaneous Rupture of the Subclavian Artery.** — ROUNTREE (*British Med. Jour.*, March 6, 1920, p. 326) reports a case of a male, well-developed, aged forty-eight years, who while pulling a sluice in a lock during rising water suddenly felt a severe pain and experienced a loss of considerable power in the right arm. There was no swelling and no mark of injury, but five weeks later, when examined, the extremity was cold and pale. There was no muscular wasting and all the ordinary movements could be carried out with precision. No pulse could be felt anywhere from the axilla downward. The subclavian pulse could be felt and was equal to that on the other side. A week later color and warmth and a good deal of power had returned. The right radial pulse, although smaller than the left, was palpable. Two years later the pulse was better and could be felt throughout the limb. There was no sign of aneurysm. The author thinks the case was a rupture of the inner and middle coats of the vessel where it crosses the first rib.

**The Repair of Cranial Defects by Autogenous Cranial Transplants.** — COLEMAN (*Surg., Gynec. and Obst.*, 1920, xxxi, 41) says that in a series of 208 patients, with head wounds, under observation at U. S. General Hospital No. 11, 53 patients were operated upon for the repair of cranial defects. The study of this group of patients provides data for estimating the influence of a skull defect as a factor in the disability of patients with head injuries. The cranial defect may be of slight importance in comparison with the associated brain lesions. The symptoms may be modified to some extent by a cranial defect, and cranioplasty may give a certain amount of relief; but, as a rule, repair of the defect does not benefit conditions resulting from structural brain damage. Scrupulous regard for the limitations of cranioplasty are necessary. These operations should seek to do two things, protection of the brain and relief of deformity. It is the fluctuation of the defect, in various positions, which is mainly responsible for the symptoms which are very characteristic. These patients are disinclined to exercise and suffer disturbed sleep because of throbbing or vertigo when lying in bed. The author says that the symptoms are explained by the local instability of the brain mass, the traction of the adhesions and the associated vascular fluctuations. Cranioplasty should not be attempted until the wound has been healed for three months. Any associate intracranial process accompanied by an increase in tension, intracerebral foreign bodies and sometimes epilepsy make the operation inadvisable. The author used the Charles H. Frazier method of autogenous cranial transplantation. The scar tissue is removed and the dura freed from the bony rim, which is then bevelled with a fine chisel. The dura is not opened. A pattern of the defect is made and placed on the parietal eminence of the same or contralateral side and a thin lamina of the outer table with the overlying pericranium, removed. The graft is molded into the desired curve and fixed with fine interrupted catgut sutures. The patient is kept in bed for two weeks, allowing the horizontal position to give the graft the proper curve. The cranial bones heal without much callus formation. In patients with extensive scars a plastic on the scalp should be done first. The improvement in patients operated by this method is striking.

**Homotransplantation of the Kidney and Ovary.**—DEDERER (*Surg. Gynec. and Obst.*, 1920, xxxi, 45) has transplanted the left kidney and ovary together with their blood supply from one puppy to the neck of another of the same litter. Circulation was continuous with the exception of forty-two minutes, during which time the organs were simply left out in the air in the field of operation. On the evening of the same day urine flowed from the ureteral orifice, in spite of the fact that urine was also being excreted by its own two kidneys. This continued as long as the dog lived. The dog died on the twenty-eighth day following an operation for intussusception. The transplanted organs were removed under operative conditions and were tested as to transplantability by anastomosing the renal vessels to the splenic vessels of another dog. This was only partially successful. The author concludes that it is possible in making a homotransplantation to get a satisfactory arterial anastomosis by suture when the renal artery is less than 1 mm. in diameter. The transplanted kidney passed the same functional tests and reaction to severe constitutional infection as are required of a normal kidney.

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**Apparent Spontaneous Rupture of a Normal Spleen.**—SHORTEN (*British Med. Jour.*, December 27, 1919, p. 844) reports a case of a soldier, aged forty-three years, who while walking was suddenly seized with acute abdominal pain, localized about the umbilicus. It was so severe that he fell to the ground. He vomited and the pain subsided enough to allow him to walk to his billet. He carried on his duties for four hours and then reported sick. He was given a dose of castor oil, which he vomited. At 6.30 P.M. he arrived at the hospital in collapse, temperature 96.8° F., pulse 130 and feeble. There were no signs of injury. The abdomen was tender and there was board-like rigidity. His legs were drawn up. Both flanks were dull. There was no previous medical history bearing on the case. The diagnosis of a ruptured viscus was made and the patient was operated on under ether anesthesia at 10 P.M. Splenectomy was performed. Hypodermoclysis was given continuously during the operation. Examination of the spleen disclosed a rupture through the hilum. The recovery was uneventful, the patient being evacuated to England four weeks later.

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**Traumatic Rupture of the Heart.**—HOWAT (*Lancet*, 1920, 1, p. 1313) reports a case of traumatic rupture of the heart, liver and kidney in an adult male, aged twenty-three years. The man fell forty-five feet, alighting on a wooden plank and a pile of steel plates. The death was not instantaneous, the patient dying twenty minutes after the accident in a hospital. Externally there were practically no evidences of injury. Autopsy revealed a badly lacerated liver. There were about two and a half pints of blood in the peritoneal cavity. The right kidney was torn in two places and there was extensive retroperitoneal hemorrhage. The pericardium was distended with blood, due to a rupture of the free edge of the left auricular appendage.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

**A Case of Chorea Complicated by Gangrene of the Fingers.**—CHODAK (*British Jour. Children's Dis.*, July-September, 1919) reports a case of a girl, aged twelve years, who was admitted to the hospital suffering with chorea of a week's duration, and with no history of an antecedent attack. Ten days later the right hand became white and the fingernails blue. In the course of a week gangrene of the finger tips and the ball of the thumb had definitely set in. The pallor spread up the arm. There was no pulse at the wrist, but the brachial artery could be felt pulsating about half way down the arm. The pain became severe. Later the brachial pulse disappeared slowly from below upward and the brachial artery could be felt like a thick cord along the arm. The choreic movements subsided soon after the gangrene began. The gangrene began to fade early and was checked with some loss of function of the hand. There were three possible causes: embolism, arteritis leading to thrombosis, and arterial spasm. The writer inclines to the arteritis being the cause although he draws no absolute conclusion to that effect. There have been other cases of gangrene of the extremities following chorea reported in the literature.

**Feeding Solids to Sucklings.**—LOWENBURG (*New York Med. Jour.*, January 3, 1920) analyzes the records of 128 cases to ascertain at what ages solids were first given and to note the effect upon alimentary function and nutrition. Of these, 76 received solid food between the ages of six and eight months. He says that the food elements, protein, fat, carbohydrate, water and mineral salts exist in all foods in varying amounts. He sees no reason why these materials as they exist in the vegetable and animal kingdoms, as represented in other foods than milk, when properly prepared, may not be administered to sucklings. Thorough cooking and fine mechanical subdivision provide the means whereby foods other than milk may be made acceptable to the digestive apparatus of the infant. Babies under one year bear well a mixed diet containing comminuted solids. The best age at which to commence their use is probably at six months, although further clinical experience will probably demonstrate that it can be accomplished earlier. This has already been noted in malnutrition in either bottle or breast-fed babies. Even in very young infants of from two to three months an immediate gain occurs following the use of gradually increasing amounts of well-cooked cereals such as farina, cream of wheat, cornmeal mush and the like. The total elimination of milk, a twenty-four to thirty-six-hour hunger period, the use of a saccharated weak tea, followed by the use of the least fermentable carbohydrates (starches), and finely comminuted solids, constitute the correct treatment for diarrhea. Alkalies such as calcium carbonate and fuller's earth are useful additions in that they

check fermentation, favor putrefaction, and are excellent thickening agents. More important than the influence on weight, are the beneficent results noted with reference to mental and physical development and vigor, the increase of tissue tone, and the prevention of rickets and scurvy.

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**A Study of Achondroplasia.**—WHEELDON (*Am. Jour. Dis. Children*, January, 1920) reports 6 cases, which he places in two groups. Three cases comprise the first group, in which the symptoms of dwarf growth were more prominent. In the second group are 2 cases, which showed the symptoms of infolding. The sixth case showed symptoms falling under both classifications. The 2 cases of the second group have a feature, which has never been described before, no mention of it being found in the literature. Each of these cases showed an arcuate kyphos with a point of greatest convexity. In 1 case it was in the dorsal region while in the other it was in the dorsolumbar. Roentgen ray showed a wedge-shaped vertebra at the point of greatest convexity. No disease of the spine could be found, so that the author took the stand that this peculiar vertebra was the result of Jansen's "amniopressure." The same force which presses on the two ends of the spine producing the kyphos might also very easily produce the wedge-shaped vertebra. Two cases of the first group had in addition to the ordinary symptoms of achondroplasia, certain bony changes which could be shown in the roentgen ray. The author believes that these changes are similar to those described by Ehrenfeld. The name achondroplasia was chosen for this condition because the state is an aplasia of chondrium. It is characterized by symptoms of dwarf growth such as shortening of the extremities, vertebral column and chest and looseness of the skin, and also by symptoms of infolding, such as kyphosis base os cranii, sagittal narrowing of the foramen magnum, depression of the nasal bridge, narrowing of the choanæ, reduction in the size of the sella turcica with consequent reduction in size of the pituitary body, and changes in the spine. The changes are probably due to the smallness of the amnion except in rare cases. The pathologic changes consist mainly in a retardation of ossification of the epiphysis and diminished production of endochondral bone, while the periosteum produces a comparatively normal amount. These changes of achondroplasia are produced between the third and eighth weeks of intra-uterine life. Besides the deformities of the bone, the characteristic roentgenologic appearance of a long bone under examination shows that near the epiphyseal ends the diaphyses become cup-shaped producing a T-shaped outline without any disturbance of the epiphyseal line or zone of proliferation, though these may be uneven and take on more or less fantastic shapes as compared with those of a normal individual. All of the cases presented in this paper bear out all that has been said and in addition two of them show a new symptom, a wedge-shaped vertebra, which falls in the symptoms of infolding and fortifies the belief that the state of achondroplasia is produced by the smallness of the amnion.

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**Calcium Metabolism of Infants and Young Children, and the Relation of Calcium in the Stools to Fat Excretion.**—HOLT, COURTNEY and FALES (*Am. Jour. Dis. Children*, March, 1920), in this, their second

contribution on this subject, take up the study of children on a mixed diet. They found that with children taking a mixed diet, the absorption of calcium per kilo was lower than that of children taking modification of cow's milk, averaging, when the intake was adequate, 9.955 grams of calcium oxide per kilo. The average daily excretion of calcium oxide in the stools of children taking a mixed diet was 0.87 gram. In regard to the calcium absorption and excretion in relation to fat intake, it was found that the calcium oxide intake per kilo in children taking mixed diets was lower than that of infants, the average for 79 cases being 0.108 gram per kilo. The absorption of calcium oxide when the intake of calcium oxide was more than 0.09 gram per kilo in nearly every case exceeded 0.03 gram per kilo, with an average of 0.055 gram. When the intake was only 0.09 gram per kilo or less the absorption rarely exceeded 0.03 gram per kilo, and in several cases there was a negative balance, the average being only 0.015 gram. The percentage of the calcium intake absorbed when the intake exceeded 0.09 gram per kilo averaged 40.4 per cent.; when the intake was 0.09 gram or less the absorption generally averaged only 20.3 per cent. The inference may, therefore, follow that an intake of at least 0.09 gram of calcium per kilo is necessary to ensure a good absorption by children taking a mixed diet. The best absorption of calcium oxide was observed when the intake of fat exceeded 3 grams per kilo, and when at the same time for every gram of fat there was in the diet from 0.03 to 0.05 gram of calcium oxide. This is a somewhat lower proportion of calcium oxide to fat than was needed to ensure good absorption of calcium oxide by infants taking modifications of cows' milk. When calcium in the form of chalk mixture (calcium carbonate) was added to the diet there was a greatly increased absorption of calcium. When calcium was added in the form of calcium acetate or as calcium phosphate the absorption was not increased. The excretion of calcium was not so closely related to the intake of calcium as in the case of infants taking modification of cows' milk, and was not related at all to the fat intake. A very small intake of calcium resulted either in an absorption not much greater than the amount normally excreted or in a negative balance. The excretion of calcium in the stools was not at all related to the excretion of fat, but bore some relation to the excretion of fat as soap. However, in the constipated stools, which contained the most soap, the calcium excretion was not as great as in the normal stools when the intake of calcium oxide was the same. The calcium lost as soap in the stools of normal children taking a mixed diet was in most cases an insignificant part of the calcium intake. The calcium formed a small part of the total solids of the stools of infants taking modifications of cows' milk. The calcium percentage of total solids was lower in acid than in normal or constipated stools. The two factors chiefly affecting the percentage of calcium in the stools of children taking a mixed diet were the amount of calcium intake and the reaction of the stools. The soap percentage of the total solids followed on the average the variation in the calcium percentage of the total solids. The absorption of calcium by children with chronic intestinal indigestion was extremely low. In the only instances in which the absorption was near the normal both the calcium and fat intake were high. The

excretion of calcium in the stools was very high, except when the intake was unusually low. The excretion of total fat and of fat as soap was very high, but was not paralleled by the calcium excretion. The calcium absorption of children with acute rickets was lower than that of children who were normal, even though the calcium intake was ample. The calcium excretion in the stools was somewhat higher than the average excretion in the stools of normal children. During recovery from rickets the absorption of calcium was higher than the average for normal children. This improvement accompanied the taking of cod-liver oil or additional butter, with a diet containing an ample amount of calcium. The calcium excretion in the stools of children recovering from rickets was lower than that in the stools of normal children. Cod-liver oil increased the absorption of calcium, except in cases in which the intake of calcium or fat was very low. The substitution of vegetable fats for milk fat did not affect the calcium metabolism of children taking a mixed diet.

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**An Early Diagnostic Sign in Basilar Meningitis.**—GINGOLD (*Arch. Ped.*, January, 1920) reports a case illustrating this diagnostic sign of early meningitis. He calls this a "reflex" strabismus. It is elicited by flexing the head on the chest. When this is done either a bilateral or unilateral strabismus develops which will last as long as the head is kept flexed and disappears as soon as the head is relaxed. In many cases the strabismus is accompanied by a retraction of the upper eyelids. He has also noticed a contraction of the pupils in some cases. During a period of seven years of observation "reflex" strabismus was present in the early stages of almost every case that came under his observation. In the late or paralytic stage flexion of the head fails to produce strabismus. By means of this sign he has been able to make a diagnosis of basilar meningitis days before any other meningitic symptom appeared. The difficulty of making a positive diagnosis of tuberculous meningitis in the early stages of that disease is well known. In most cases onset is gradual, and the symptoms are vague and indefinite. There may be no other sign than those of vague digestive disturbance for days or weeks. The diagnosis is especially difficult in young infants since the yielding cranium keeps the intracranial pressure below the fatal limits and often weeks will pass before definite signs appear.

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**Clinical Interpretation of Scarlatinoid Rashes.**—SCHOLTZ (*New York Med. Jour.*, February 21, 1920) offers an interpretation based upon a study of symptomatology, pathology and pathogenesis. He says that scarlet fever rash is not a well-defined and distinct dermatological entity and cannot be differentiated from the rest of scarlatinoid rashes; it is merely a specific type of toxic scarlatinoid erythemata. Scarlatinoid erythema is not an independent clinical entity but merely a symptomatic erythema caused by all varieties of systemic toxins. The differentiation of scarlatinoid erythemata cannot be made on purely dermatological grounds, but essentially on the associated symptoms and the mode of development. Nosologically scarlatinoid erythemata should be regarded as erythematous types of the great generic group of erythema multiforme.

## OBSTETRICS

UNDER THE CHARGE OF

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**Uterus Bicornis, with Two Ova Implanted in One Horn and a Fibroid in the Other.**—CORNELL and EARLE (*Surg., Gynec. and Obst.*, November, 1919) report the following unusual case: The patient had been in poor health, with colic-like pain in both lower quadrants of the abdomen. She had had a severe cold and coughed considerably. She had noticed a bloody, vaginal discharge, which finally ceased. She felt very heavy under the vaginal region while walking and complained of severe pain in the lower abdomen, especially on the left side. She had had several children and several miscarriages, and had not previously been pregnant for ten years; but during this time she had not felt well, although a diagnosis of pelvic disease had never been made. On examination the patient was in fair, general condition, with badly lacerated perineum, a small cystocele and rectocele. There was but one cervix which had been lacerated. On the left side there was a soft, boggy mass about the size of a grapefruit, which was tender and freely movable. Slightly to the right of the median line another globular mass was found, which was hard and thought to be the body of the uterus. This was later found to contain a moderate sized fibroid. The right tube and ovary could be easily palpated; the reflexes were normal throughout; there were no varicosities; temperature, pulse and respiration were normal. A probable diagnosis was made of ruptured ectopic pregnancy, with fibroid uterus. At operation two uteri were found, each about the size of a grapefruit. Each had only one tube, with one ovary attached to it. Evidently one of the uteri was pregnant while the other contained a fibroid tumor. Both cornua with ovaries and tubes attached were removed intact at the junction with the cervix. The left ovary contained the corpora lutea, the right ovary was normal, and was divided in one portion in the peritoneum, the other in the rectal fascia. The abdomen was closed in the usual manner. Subsequent examination showed that the hemorrhage had come from the pregnant uterus. It had evidently proceeded from an incipient abortion. The patient was seen afterward and stated that she had suffered burning pains shortly after she left the hospital. She had many of the symptoms of the menopause, but not as severe as those usually experienced. The area around the ovarian graft in the rectal fascia was normal. The ovarian graft could not be felt nor was there tenderness. On vaginal examination the small portion of the cervix was in good position, but on the left side was a cystic swelling, probably connected with the round ligament. It was not painful. On examination it was found that two ova had been implanted in the pregnant uterus and that their implantation had been so low as to threaten abortion. One ovum was considerably larger, with better developed placenta, than the other indicating that it was several days at least older. One corpus luteum was solid, the other hollow, which would indicate that one was considerably older than the



other. The chorion of one ovum was abnormally small as compared to the embryo and the condition of the ovum and placenta indicated inadequate nutrition. There was a greater amount of lutean tissue in one corpus luteum. It is a somewhat extraordinary fact that during a number of years of more or less ill health the patient had visited clinics frequently and no adequate pelvic examination had been made.

**The Analysis of the Signs and Symptoms of Early Ectopic Pregnancy.**—HEANEY (*Am. Jour. Obst.*, 1919, p. 17) draws attention to the neglect of cases of early unruptured ectopic pregnancy. In teaching, emphasis is usually placed on advanced and critical cases where rupture has occurred. The student does not suspect ectopic pregnancy, except in the extreme and critical cases. Unless threatening symptoms are present he does not think of this complication. Every patient who presents herself with suspicious symptoms of threatened, imminent or incomplete abortion should be examined, with the possibility in mind that the condition will not be an ordinary abortion, but an ectopic pregnancy. It is specially significant that the cramp-like pains are located at the seat of the pelvis instead of over the uterus. Undue emphasis is also placed on the passage of a uterine cast or small portion of the decidua. In many patients this is never seen. While it is ordinarily taught that the uterus enlarges in ectopic pregnancy, operation shows no appreciable increase in a considerable number. In some patients the uterus is abnormal, while these cases frequently occur in patients in whom the uterus and tubes are undeveloped and in whom ectopic pregnancy is especially liable to occur. Rupture frequently occurs before the tubes are sufficiently enlarged to be recognized by bimanual examination. Failure to palpate a supposed gestation sac in a case of shock and pain should not deter us from operating on an otherwise clear case. The symptoms of a ruptured tube are usually portrayed in an exaggerated manner. The amount of shock depends upon the quantity of blood lost, not merely upon the rupture of the tube. If only small vessels have been severed and the lesion is a small one the patient may have sudden pain, but not necessarily shock, and the pain will be followed by some nausea and weakness. Any woman in the child-bearing age who is seized with abdominal pain of severity, followed by shock or syncope, even though these symptoms be brief, must arouse the suspicion of ectopic pregnancy. Leukocytosis and a normal or subnormal temperature should lead to the diagnosis of probable ruptured ectopic pregnancy when there has been severe abdominal pain, followed by nausea and perhaps vomiting. Exploratory vaginal incision should be practised more frequently in doubtful cases. If a case is sufficiently suspicious to be in a hospital a definite decision should be made, and this can readily be accomplished by a vaginal incision. If there be any ectopic pregnancy the danger to the patient is slight and is more than made good by the accuracy in diagnosis.

**Glycosuria in Pregnancy.**—CAMERON (*Canadian Med. Assn.*, January, 1919, p. 723) in studying the case of a patient in her fifth month of pregnancy found a small quantity of the reducing sugar in the urine. After the sixth month this disappeared and it was concluded that this was a transient lactosuria. The confinement was tedious and nearly

two ounces of chloroform was used. The puerperal period was uneventful. Within a week from this time the patient developed signs of acute diabetes, and died of diabetic coma three weeks later in spite of vigorous treatment. Since seeing this case in the material of 468 obstetrical cases the writer had four in which there was glycosuria. It is true that lactose and glucose may appear in the urine, with no more significance than demonstrating a normal stimulation of the mammary glands, as they are prepared for lactation, and these substances will often disappear from the urine after lactation is established. In other cases, however, this does not happen and the excretion of sugar in any form or amount shows derangement in metabolism, and when to this disturbance in metabolism a pregnancy is added the condition becomes greatly complicated. There can be no doubt but that the finding of the reducing sugar in the urine of a pregnant woman is a serious matter. Lactosuria is unimportant, but when the patient's urine reduces the copper hydroxide in a test solution the fullest test should be made to determine whether lactosuria is a real condition or not. If there is glycosuria true diabetes may be about to manifest itself or may be already present. Although the sugar may disappear from the urine during pregnancy the patient should be kept under observation afterward. Diet should be carefully regulated, and if the patient comes into labor and requires an operation the choice of an anesthetic is a critical one, and attention should be given to lessening the shock of delivery, and thus delaying the formation of important changes in the organism of the patient. When the regulation of diet does control glycosuria the diagnosis of true diabetes becomes very important. While the frequent examination of the urine is useful and thus furnishes the only means of arriving at definite conclusions by estimating the sugar in the blood with a proper calorimeter the method is simple. Whenever sugar appears in the urine the presence or absence of hyperglycemia should be determined. It may be difficult to induce a patient to use ingestion tests of the carbohydrate.

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**Pregnancy Complicated by Ileus.**—HANSEN (*Ugesk. f. Læger*, 1919, lxxx, 356) has studied the literature of this subject and has collected the reports of 102 cases of ileus complicating pregnancy, of which 57 proved fatal. Operation was done in 64 cases, with a mortality of 45 per cent. and 38 cases were treated without operation, with a mortality of 71 per cent. This condition is usually caused by the formation of adhesions in the abdomen following some previous operation. The pressure of the pregnant uterus on the bowel brings about this complication in a few cases only. There is a difference of opinion concerning the wisdom of emptying the pregnant uterus in an operation for ileus. In a series of 33 cases reported by one author the abdominal operation was followed by abortion in 24, and this writer recommends the emptying of the uterus by vaginal Cesarean section. Hansen records two of his own cases: The first was that of a multipara, aged thirty-seven years, whose last child had been born thirteen years previously. Since then she had been operated upon for ectopic gestation. Shortly after her last period she had violent abdominal pain. Other symptoms of intestinal occlusion developed, and she was brought to the hospital. At operation a thick, fibrous band was found which was strangulating the small intestine, and was excised. The patient was discharged well a month later and gave birth spontaneously at full term. The second

case was that of a woman, aged twenty-five years, who five years previously had appendicitis and operation. She was six months advanced in her last pregnancy and she was brought to the hospital with symptoms of intestinal obstruction. When the abdomen was opened there was found a fibrous band passing over the small intestine near the ileocecal valve and the transverse colon, and over this band the small intestine had become kinked. The band was tied and removed. The patient made an uneventful recovery, went to full term and gave birth spontaneously. In both of these patients the uterus was left undisturbed.

**Toxemia of Pregnancy Treated by Standard Methods.**—MOSHER (*Jour. Missouri Med. Assn.*, 1919, p. 1669) describes his experience in forty-four pregnant women suffering from various degrees of toxemia. A considerable number of these cases occurred in a comparatively short time. When an effort is made to account for this it is found that the season of the year was unfavorable, as there were extreme changes in temperature and moisture, and that at this time the people of the United States were subjected to great excitement through the development of the recent war. All patients are examined with a view to detecting the signs of threatened toxemia. Blood-pressure is taken, eye symptoms are noted, the urine is examined and the teeth and tonsils are inspected as possible foci of infection. Clinically speaking the writer believes that eclampsia results from the failure of elimination of toxins. In the early portion of pregnancy he believes these toxins are formed in the placenta, while later they arise from the excretions of the fetus. Acute infections of various sorts predispose to toxemia through the additional burden thrown upon the pregnant woman. Asphyxia resulting from pressure, congestion, decrease in the natural oxygenation of the woman's blood, due to interference with the expansion of the lungs and the action of the heart, may also predispose to toxemia. Whenever eclamptic convulsions develop some focus of infection will be found. In prophylactic treatment the writer believes that a diet of non-irritating food is of primary importance. The action of the bowels, kidneys and skin must be stimulated and the intake and output of fluid should be carefully observed and recorded in a daily report. Care should be taken to eradicate foci of infection in the tonsils, teeth, kidneys and bowels. Deep breathing in fresh air and stimulation of the general circulation are important. The free giving of alkaline salts and food to prevent acidosis is of value. Should blood-pressure be high, veratrum viride may be given to reduce pressure, lessen the pulse-rate and aid in the action of the skin. When a patient grows worse under such treatment the uterus must be emptied. This should be done in the least irritating way, and should be carried out promptly so soon as prophylactic treatment fails. The prompt improvement of the patient after this operation is a fact familiar to all. Ether anesthesia is employed, as this is the only safe anesthetic for use in these cases. The writer's method consists in preliminary gradual dilatation by solid dilators up to No. 20 and then introducing a Voorhees bag No. 4 if at term. After the dilatation has reached a point when vaginal delivery can be accomplished without serious laceration the bag is removed and the patient advised to deliver herself if she can do so. If spontaneous labor fails she is delivered by forceps. Moderate hemorrhage from the uterus is encountered.

## GYNECOLOGY

UNDER THE CHARGE OF

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**Prolapse of the Uterus.**—From the observation and experience gained in the treatment of fifty consecutive cases of prolapse of the uterus during the past six years, as well as from watching and seeing the results of other types of operation for prolapse, COVENTRY (*Minnesota Med.*, 1920, iii, 286) believes that his results give by far the greater percentage of cures, not only anatomically but also symptomatically. In those cases coming under first degree, or as one might say, in those cases headed toward a prolapse, he prefers the Baldy-Webster operation, and repair of the perineum and cystocele has been sufficient to give the patient a great deal of comfort and to cure these cases. In the second and third degree prolapse cases, one must here use some judgment before deciding on the exact type of operation that one wishes to do. As said before, cystocele invariably is present. In these advanced cases he believes that there is only one type of operation that combines safety, comfort to the patient, and the largest percentage of cures, namely the interposition operation, whether after the so-called Wertheim-Watkins or the so-called Mayo method. If the uterus is of good size and not atrophic he prefers the former: if atrophic, by all means the Mayo method. It may not here be amiss to go into detail as one proceeds with the operation. After thorough application of iodine, the cervix is grasped with tenaculum forceps, and an inverted "T" incision made in the anterior vaginal wall. Then by gauze and blunt dissection the bladder is readily freed, both laterally and anteriorly. There is practically no danger of injuring the ureters, because before you come to them you will undoubtedly get into a plexus of veins which, however, one should guard against rupturing if possible. The bladder is now freed from the anterior uterine wall and the anterior cul-de-sac entered, taking great care not to tear into the bladder. Many times one can determine at this point whether he should do the Wertheim-Watkins or the Mayo type of operation. If the Wertheim-Watkins operation, the fundus of the uterus is grasped and pulled down and out so as to expose it at the vulva. At this stage, if one should have adhesions posterior, they can be freed, or if fibroids should be encountered they may be taken care of as one thinks best. After the uterus has been pulled forward and the bladder has been shoved up, the anterior peritoneal flap is now stitched to the posterior uterine wall. At this stage the uterus is practically extraperitoneal. The redundant anterior vaginal wall is now excised, and by interrupted

stitches, which include the anterior uterine wall, the anterior vaginal wall is closed. The vaginal wound is then closed. In closing the anterior vaginal wound, two important stitches must be inserted: (1) The most anterior stitch must be so placed as to pass through the vaginal wall picking up the deep fascia lying laterally to the urethra, and then passing through the fundus rather high up, coming out in the reverse order on the other side. This tucks the bladder well up and places the fundus snugly under the pubes. (2) The other stitch of importance is the one in the anterior cervix, placed so as to make a firm union of perimetrium, uniting in front of the cervix, and in this way the cervix is pushed well posterior. The short arm of the vaginal incision is now stitched laterally, so as to elongate the anterior vaginal wall. The cervix may be repaired or amputated as one sees fit, but here it must be borne in mind that the bladder is often dragged far down on the anterior wall of the cervix, especially when elongated. If one proceeds to do the Mayo method the short arm of the inverted "T" incision is carried around the cervix and a vaginal hysterectomy is done, the broad ligament and the perimetrium being united in the center, and this brought down as a shelving portion, taking the same place that the uterus takes in the Wertheim-Watkins operation. This elevates the bladder and gets rid of the cystocele at the same time preventing any hernia of the pelvis. The next, and very essential step, is the repair of the perineum.

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**Radiation of Uterine Cancer.**—For purposes of classification and treatment, BOGGS (*Am. Jour. Roentgenology*, 1920, vii, 202) divides cancer of the cervix into four groups: (1) Early cases, where the growth or ulceration is limited to a part of the cervix and does not extend into the vaginal wall. Even in these early cases recurrences take place, and even metastases into the glands may have occurred before the operation. (2) Where the process is more advanced and clinically the involvement is still limited to the tissues of the uterus because the organ is freely movable. Cases of this class may include cauliflower growths, which protrude from the cervix and often fill the greater part of the vagina. Even in these cases the cancer cells may not have reached the pelvic lymphatics. This is a class which will derive great benefit from ante-operative treatment, and by such procedure the end-result should be better. (3) Where the disease is further advanced and the carcinoma extends into the vaginal wall. There is slight fixation of the uterus, but clinically there is not extensive involvement of the broad ligaments. If there is no glandular involvement, which we can never determine clinically (although, as before stated, the glands are often free in cases of this class), rather a high percentage may be clinically cured by radium treatment. Time alone will tell whether or not we should depend upon radium alone, even if we have obtained brilliant results by radium in a number of instances. (4) Cases of carcinoma of the cervix, with marked fixation of the uterus, the disease extending into one or both broad ligaments with involvement of the vaginal wall and the greater part of the cervix destroyed. In many of these cases glandular involvement has taken place and in some instances metastases have extended into the liver. These cases often will derive a great deal of benefit from radium and a local or clinical cure frequently will take place. But even if

metastases have been extensive the patient may remain free from cancer symptoms from one to three or more years. A cure might be effected, but with our present method of treatment we always expect the patient to die from metastases rather than look for a permanent cure. When it is considered that about one-third of the cases of cancer of the cervix that receive no treatment die within a year without an operation, that a large percentage of the remainder die within two years from the first manifestation of the disease and that very few live three years, it is apparent that the amount of palliation and prolongation of life from radium treatment (and the fact that many of them die of internal metastases without return of the local symptoms), mean much to the patient. Today radium is indicated as a palliative measure for hopeless inoperable and recurrent cases as an anteoperative procedure and for prophylaxis after surgical removal. Lately radium is being used by some physicians for primary cases in carcinoma of the cervix when the disease extends into the cervical canal, because nearly all of those cases are followed by recurrence even in the early cases after operation. The malignant process in these cases will disappear by radium rather promptly. Time alone will tell whether radium without operation is advisable. Radium is a specific palliative in operable cancer of the cervix and uterus. It will clinically cure some of the cases, and subjective improvement is noticed in a certain percentage of others. However, recurrence takes place in many of these clinically cured cases within two or three years. The patient during this interval regains normal health and can lead a useful life. If a recurrence takes place, as a rule, the patient suffers little in comparison with those who had no radium treatment. In these hopeless cases, the offensive discharge and hemorrhage usually completely disappear within from two to four weeks. The cessation of discharge which often is so offensive to the family and even to the patient is a remarkable feature. The local condition changes in character within from two to four weeks after the treatment, the mass begins to contract and shrink, and continues to decrease in size. This is more marked in some instances than in others. The deodorizing and sterilizing effect of radium is very remarkable in the inoperable or recurrent cases where there is a broken down mass of carcinomatous tissue or a crater-like sloughing extending into the broad ligament. These cases have a discharge with a very foul odor and run an irregular temperature. One application of radium will alleviate these symptoms and means much to the patient.

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**Vaginal Palpation of the Ureters.**—The normal ureter, according to Judd (*New York Med. Jour.*, 1920, cxi, 986), is easily palpable from the side of the pelvis, just above the spine of the ischium, although in some cases it lies as much as 4 cm. above the spine, where it lies underneath the peritoneum and previous to entering the broad ligament in the course of its entrance into the bladder. Undoubtedly in the case of a thickened ureter from ureteritis, or from any cause whatever, it can be easily palpable to a far greater extent, as has been exemplified in some of his own findings. Contrary to the general method advised, which is that palpation be made for the ureter in the anterior vaginal fornix, he suggests beginning at the lateral vaginal fornix, using the left index

finger for the left ureter and the right index finger for the right ureter. The normal ureter presents itself as a slender cord, with its convexity outward, and with a restricted mobility, due to its anatomical relationship with the peritoneum and side of the pelvis. It is smaller than a goose quill, feeling about the size of an ordinary shoestring. It is best palpated by sweeping the finger above the point of its location and then slightly bending the end of the finger, as one might in picking the strings of a guitar, sweeping them down over the ureter, straightening the finger out and going back and bending it again before going down, always getting the feel of the ureter from above downward and not from below upward. Palpation of the ureters opens a great diagnostic field. Among conditions discoverable, according to Judd, are the following: An acute ureteritis, diagnosed by simple tenderness along the line of the ureter. Chronic ureteritis and periureteritis are shown by tenderness and thickening, the greater the extent of the periureteritis, the greater will be the lessened mobility of the ureter. Tuberculosis of the ureter and kidney gives a thickened, nodular feeling with tenderness and restricted mobility. Calculi and gravel in the ureter furnish a most brilliant field for diagnosis. It is Judd's belief that these conditions can often be detected where the wax-tipped ureteral catheter fails to disclose a stone, particularly where the stone is smooth and pocketed.

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**Contra-indications to Nephrolithotomy.** — Before deciding upon operation in cases of stone in the kidney or ureter, BRAASCH (*Minnesota Med.*, 1920, iii, 387) states that we should consider the duration of symptoms, the size, situation and number of stones, the question of bilateral lithiasis, the renal function and complications in other organs. The duration of symptoms should be a considerable factor in determining the advisability of immediate operation since it is not generally realized that probably 75 per cent. of renal stones pass spontaneously. The majority of these stones will probably pass within three or four months following the first symptom. It may be stated, therefore, that it is usually inadvisable to operate for a stone in either the kidney or ureter until at least three months, and possibly six months have elapsed since the onset of the symptoms. Immediate operation for stone following the first or second attack of pain, without evidence of other complications, is strongly to be condemned. Nature should be given full opportunity to remove the stone without intervention. There may be exceptions to this rule, such as excessive pain continued over a duration of several weeks or months, evidence of acute perinephritic or cortical infection, and evidence of urinary retention sufficient to endanger the kidney. Moreover, when it is evident that the stone is too large to pass, nothing is gained by further delay even though the onset of symptoms is very recent. If the stone is less than 2 cm. in diameter, operation should be delayed. If the stone is situated in the cortex of the kidney, the urgency for operation is not so great as when the stone is in the renal pelvis. If multiple stones are present, it is usually advisable to operate irrespective of the size of the individual stones. In cases of bilateral nephrolithiasis, if there are no acute symptoms and the stones are large and multiple, operation is usually inadvisable. Removal of such stones situated in both kidneys is usually accompanied

by considerable destruction of the kidney tissue, and the chances are the patient would live as long and as comfortably without operation. When the symptoms are acute and unilateral, however, operation is of course indicated. Low renal function usually contra-indicates operation, although if the symptoms are very acute, operation may be justifiable even under such conditions. A renal functional test of from 20 to 30 per cent. in the presence of lithiasis, particularly when bilateral, will frequently become approximately normal after the stones have been removed. When the phenolsulphonephthalein return is only a trace, however, and the urea retention is high, operation should not be considered unless the symptoms are urgent. In cases of stone in the lower ureter, in justice to the patient an attempt should be made to dislodge the stone by cystoscopic manipulation before resorting to operation. Braasch has been able to cause the stone to pass following such manipulations in 126 cases; but he believes that when the stone has been lodged in the lower ureter for from three to six months or longer, or when it is larger than 2 cm. in diameter, the possibility of its dislodgment by cystoscopic methods is greatly diminished. Such manipulations are also contra-indicated when there is acute renal infection, intolerance on the part of the patient to the cystoscope or anatomic deformity.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**Psychiatric Studies of Delinquents.**—TREADWAY and WELDON, U. S. Public Health Service, and HILL, Special Agent of the Children's Bureau, U. S. Department of Labor (*Public Health Reports*, No. 27, xxxv, 1575) report the results of studies on the mental and medical aspects of prostitution, and draw the following conclusions and recommendations: The presence of so many psychopathic individuals among the groups studied indicates that the problem of delinquency—and particularly of sexual delinquency among girls and women—is a medico-psychological as well as social one. Moreover, the findings of this study as they relate to the make-up of these offenders show the importance of recognizing and understanding certain types of mental reactions in children, which frequently lead to the development of antisocial traits of character in later life, in order to institute suitable methods of corrective training. The findings indicate the need for an adequate system of medical supervision of children in the schools. The principles of personal hygiene should be taught; a dentist and dental equipment



provided; a specialist in diseases of the eye, ear, nose and throat should serve on the medical staff; and funds should be provided for the purchase of glasses. Similar supervision, instruction, and provision should obtain in all correctional institutions. Another important step indicated is that medical supervision of school children shall be made to include not only the discovery, correction and prevention of physical defects, but the detection, also, of such tendencies of behavior as those referred to above, which may later develop into serious defects of mind and character. Such inspection should be part of the State health program, and this program should also make reportable feeble-mindedness and certain forms of insanity. Since mental defect is so conspicuous in cases of delinquency, the importance of mental hygiene is evident in the control of delinquency as well as in the control of venereal diseases. Supervision of the mentally defective in the community—the establishment of special classes in public schools for training mental defectives and delinquent children—will also serve to prevent delinquency and the social ills caused by inadequate care of the feeble-minded. The level of intelligence is likely to be low among delinquent women. Among the group studied it varied considerably. Cognizance must be taken of this fact in establishing a school for their training. Moreover, the difference in mental attainments suggests that individual training should constitute, in large measures, the method of such a school. Further, the frequent concurrence of mental disorders among the group studied indicates that provision should be made in special State institutions for those children who are unable to profit by special school classes and for those feeble-minded, epileptic and insane persons who exhibit distinct antisocial tendencies. Similar provision should be made for psychopathically inferior individuals not generally recognized heretofore as in need of institutional care. The mental status of all individuals in correctional institutions should be considered by a medicopsychologist before they are paroled, and a medicopsychologist should serve in the juvenile and adult courts for the purpose of securing proper mental classification of offenders, thus preventing injustice in disposing of their cases. A State institution for the feeble-minded which admits only those idiotic and imbecile persons under fifteen years of age who are incapable of instruction in the public schools is not an adequate provision for all those mentally defective individuals who complicate the delinquency problem. Proper care and protection should be given also to the feeble-minded who are actual delinquents or likely to become so. By this means the danger to society in general would undoubtedly be lessened. The cost of adequate provision for the feeble-minded would be less than the cost to the community of their neglect and consequent antisocial conduct. The Kansas Legislature recently passed a law allowing the commitment of mentally defective delinquents to the State institution for the feeble-minded without the consent of parent or guardian. This study has made clear the necessity for such provision. In public and private relief agencies mental examinations by a competent psychologist or psychiatrist should be given members of families coming to their attention, especially those furnishing difficult problems. Such an examination not only would be of great assistance to the agency in making adequate plans for treatment, but also would prove

helpful in many cases by giving a starting-point for the diagnosis of causes of immorality in the cases of certain specific individuals. It is a shortsighted policy which refuses to admit to an industrial school delinquent girls suffering from venereal diseases, but makes no other provision for the training or care of such girls. While it serves the immediate purpose of protecting the girls already in the institution, it allows to remain unchecked sources of danger to public health and to the social standing of the community. Neither is that policy adequate which quarantines the girl until the infectious stage of the disease is past and then turns her back into the community. Morally delinquent girls should, where the evidence warrants, be committed to an industrial school, whether venereally diseased or not; subsequent to commitment, but prior to mingling with girls already within the school, infected girls should be given treatment until danger is past in a quarantine cottage attached to the school or in some other designated place. Where morally delinquent girls and women are quarantined in the same institution the juvenile and adult delinquents should be cared for separately. It is unfortunate that in the present situation children as young as fourteen must, because of the necessities of the method of providing medical treatment, associate with older and more hardened women. The age through which girls are protected by laws in regard to age of consent is an important factor in lessening immorality. The legal age of consent in Kansas is eighteen years, yet though 29 of the girls included in this study were under eighteen years of age at commitment, and at least 56 (all but 10 of those for whom the age at first lapse from moral conduct was known) had been first immoral before reaching the age of eighteen, there is no evidence to show that any man was brought into court for violating the law in regard to age of consent in respect to any one of these girls. The man's responsibility for contributing to a girl's delinquency and for the spread of venereal disease should be better recognized, and the man should be punished as well as the girl or woman. It was known that 2 of the inmates of the Kansas State Industrial Farm at the time this study was made had become diseased through the same man, yet the man was allowed to go free. While some measure of correction may be required, moral delinquency can be curbed better by preventive than by corrective measures. To be effective preventive work should be undertaken early, since the morally delinquent usually enter upon their careers when young. The inadequate supervision of children which results from the absence of a mother from her home because of gainful employment is conducive to moral delinquency. Provision which would obviate the necessity for such employment or secure adequate supervision for the children should be an effective means of reducing juvenile delinquency. Also certain economic changes whereby all women who work can earn sufficient to enable them to live in decency and comfort and have a reasonable amount of time and money for recreation will have to be brought about. Finally, these studies have shown that fundamental among the factors of prostitution are the normal and aggressive reproductive instinct of the male and the ignorance, inferiority and defenselessness of a large number of girls and women whose mental condition makes it difficult or impossible for them to make a living by legitimate means. It seems that the large majority of these women derive little or no satisfaction from their soliciting, but

follow prostitution as a sordid commercial arrangement, believing, and without doubt, correctly, that they can, for the time being, secure more compensation and physical comforts by prostitution than by engaging in any legitimate occupation which they are qualified to follow. The great majority of these women, owing to inherent defect or lack of opportunity for education and training, have extremely few interests, and can exist only by the most menial occupation. It is realized that a study of a group of delinquent women, in many individuals at least, is a study of an end-product of bad heredity or poor environment, or both, and is usually barren of immediate reconstructive results. A better understanding of such persons will require a more individual study, beginning in early childhood. To this end, as already suggested, the teacher must be interested, the school physician should have some knowledge of psychiatry, and if possible the services of a skilled psychiatrist should be utilized for consultation in the case of the peculiar or unusual child. It seems clear also that a large percentage of these women who pass through the courts and drift in and out of various penal institutions should be regarded as in some way mentally abnormal until proved otherwise by a mental and physical examination conducted by a competent psychiatrist. Modern laws relative to educational standards, with proper enforcement, will aid considerably by diminishing ignorance in those who are educable and in aiding them to a status wherein they can earn a reasonable living wage in a legitimate occupation. In the case of those who are clearly defective, and who are a menace to a community through their delinquency, there remains no solution but permanent detention under conditions where they can be made at least partly self-supporting. But after these more obviously needed changes are well on the way to solution, there will remain the problem of that great number of women who engage in clandestine or intermittent prostitution, in whom the demonstration of mental defect, to the satisfaction of the jurist, will often be extremely difficult. The history of prostitution is replete with instances of attempts at repression by the harshest measures and with little permanent result. At the present time such measures alone will accomplish but little in connection with the clandestine and occasional prostitute. The final solution of that problem is, perhaps, most of all a matter of social sentiment and conviction. Recently we have heard much about the suppression of prostitution, and the abolition of alcohol as a beverage will undoubtedly accomplish considerable good; but there will still remain, however, certain fundamental factors, such as inherent human defect, ignorance, adverse economic conditions, the power of the reproductive instinct, and the inability of many persons to live satisfactorily in the married state.

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ORIGINAL ARTICLES.

EXPERIMENTAL STUDIES IN DIABETES:  
SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION  
TO BODY MASS AND METABOLISM.

I. ALTERATIONS OF CARBOHYDRATE ASSIMILATION BY REMOVAL  
OF PORTIONS OF THE PANCREAS.

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THE preceding series of papers<sup>1</sup> gave a general outline of the checking of diabetes by fasting and restriction of total diet on the current theory of sparing the weakened pancreatic function. This speculative clinical hypothesis thus received positive physiologic and anatomic demonstration, so that the possibility of damaging the islands of Langerhans by functional overstrain and saving them by limiting the dietary burden stands as an established fact. At the same time the vagueness of this language is unfortunate and more information is desirable concerning the nature of the island function and the processes involved in overtaxing and resting it. This need is both theoretical, for understanding the endocrine role of the pancreas, and practical, for the most accurate and effective application of treatment. The same observations also afford the opportunity for such a study by furnishing plain physiologic and anatomic criteria by which the effect of various influences upon the islands can be judged.

<sup>1</sup> Allen, F. M.: Jour. Exper. Med., 1920, vol. xxxj,  
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As shown elsewhere, an explanation of the effect of fasting is not found in any gross or microscopic alterations in the pancreas; in particular there is no evidence of an increase of islands by fasting. The changes in question must be sought elsewhere in the body. The known effects of fasting and low diet are a reduction of body weight and metabolism. Each of these may be subdivided.

(a) The reduction of weight may pertain either to storage materials or to active protoplasm. It may seem natural that a reduction of stored foods should increase the capacity of the body to receive food. As a matter of fact no such rule has been demonstrable for the normal organism, particularly with reference to the most easily excreted food, carbohydrate. The utmost glycogen storage does not lower the sugar tolerance. On the contrary a dose of glucose improves the assimilation of a closely succeeding dose.<sup>2</sup> Though respiration studies indicate that fasting creates a tendency to storage of carbohydrate as opposed to combustion,<sup>3</sup> the tendency to hyperglycemia and glycosuria is notoriously increased by either fasting or carbohydrate-free diet.<sup>4</sup> Evidently some state of preparedness of the organism is here more determining than the mere fullness or emptiness of the depots.

(b) A reduction of active protoplasm may receive two opposite interpretations. On the one hand it may be supposed that reduction of the living matter which carries on metabolism will involve a reduced capacity for metabolism. On the other hand a quantitative relation may be conceived between the mass of pancreas and the mass of tissue which it can supply. As the pancreas of a mouse could not possibly suffice for the body of an elephant, the same principle may hold for less extreme differences; and when the pancreatic hormone is deficient the relatively greater supply resulting from a diminution of protoplasm may facilitate metabolism.

(c) Metabolism likewise may be variously regarded in this connection. Distinctions may be drawn between the metabolism of matter and of energy, and in the broadest sense between the exogenous or external activities of the cells and their endogenous or structural metabolism. The relation of the pancreatic function to the three chief food substances, carbohydrate, protein and fat, is also involved. In addition the influence of the other endocrine organs which affect metabolism requires consideration.

All the above relations are capable of experimental modification in various ways. Having the above criteria of pancreatic function, it is a simple matter to perform a series of experiments to furnish

<sup>2</sup> Hamman, L., and Hirschman, I. I.: *Bull. Johns Hopkins Hosp.*, 1919, xxx, 306.

<sup>3</sup> Johansson, J. E., Billström, J., and Heijl, C.: *Skand. Arch. Physiol.*, 1904, xvi, 263-272. Johansson: *Ibid.*, 1909, xxi, 1-34. Falta, W.: *Med. Klin.*, 1914, x, 9.

<sup>4</sup> Hofmeister, F.: *Arch. exp. Path. u. Pharm.*, 1889-90, xxvi, 355. Allen, F. M.: *Glycosuria and Diabetes*, 1913, Chapter XIII; *Jour. Exp. Med.*, 1920, xxxi, 557.

some information concerning this function. One group of such experiments was planned to investigate the quantitative relations of this function with the body mass and metabolism, the latter two being viewed theoretically as separate though never strictly separable in practice. Intimately connected with this problem are questions of the nature of the function: whether the quantitative relation is with food, so that a certain quantity of the internal secretion is necessary for the utilization of a certain quantity of food, or with the cells, so that they require a certain minimum quantity of the secretion, and if possessing it can metabolize indefinite quantities of food; whether the function pertains primarily to carbohydrate alone or also to protein and fat; and other questions of this character concerning the mechanism of the internal pancreatic secretion and its place in metabolism. As far as possible the experiments dealing with quantitative relations between the pancreas and the occurrence of diabetes or certain characteristic diabetic phenomena have been grouped in the present series, of which papers 1 to 4 are published in this JOURNAL and papers 5 to 12 in the *American Journal of Physiology*. Other series pertaining to the nature of the endocrine pancreatic function are presented in other journals.

The most direct means of altering the relation between pancreas mass and body mass is by surgical resections. The first experiments of the series deal with the removal of various portions of the pancreas and observations of the tolerance for Merck's anhydrous glucose by stomach and by subcutaneous injection in 30 per cent. solution. The usual precautions and standardized conditions were employed.\* Unless otherwise specified the diet was bread and soup *ad libitum* and the tests were performed after twenty-four hours' fasting. The urinary sugar was determined by titration with Benedict's solution and the blood sugar by the method of Lewis and Benedict.

#### REMARKS ON DOG B2-00.

1. The above dog received various doses of Merck glucose by stomach tube and subcutaneously after removal of successive portions of the pancreas, the standard of tolerance being the smallest quantity with which distinct glycosuria could be produced. The first removal of 7.1 gm. from the splenic end, representing between a fourth and a third of the pancreas, resulted in a perceptible lowering of tolerance by this test, so that glycosuria resulted from the injection of as little as 2.5 gm. per kgm. when it had formerly been absent with as much as 9 gm. per kgm. Further reductions of the tolerance followed the removal of further portions of the pancreas.

\* All operations were performed under ether anesthesia.

TABLE I.—DOG. B2-00. WEIGHT 14 KGM.

Date, 1913.	Glucose dosage, gm. per kgm.	Hours following injection.	Glycosuria, gm.	Plasma sugar, per cent.	Remarks.
Nov. 1	8.0	24	Faint	..	Subcutaneous injection; nor- mal dog.
8	6.0	24	Slight	..	Subcutaneous injection.
13	2.0	24	0	..	Subcutaneous injection.
17	7.0	24	0	..	Stomach tube.
20	7.0	24	0	..	Subcutaneous injection.
29	9.0	24	0	..	Subcutaneous injection.
Dec. 8	Removed pancreatic tissue weighing 7.1 gm., consisting of most of the splenic end.				
20	6.0	6	0.4	..	Subcutaneous injection.
30	4.5	24	0.3	..	Subcutaneous injection.
1914.					
Jan. 2	3.0	24	0.2	..	Subcutaneous injection.
5	2.5	24	0.2	..	Subcutaneous injection.
9	1.8	24	0	..	Subcutaneous injection.
13	4.0	14	Faint	..	Stomach tube.
		3	Faint	..	
		24	0		
Jan. 19	Removed processus uncinatus weighing 4 gm.				
Feb. 5	2.0	54	Faint	..	Subcutaneous injection.
		24	0		
11	1½	4	Slight	..	Subcutaneous injection.
		24	Faint		
Mar. 26	1½	6	Faint	..	Subcutaneous injection.
		24	0		
April 3	2.1	24	Faint	..	Subcutaneous injection.
20	2.4	6	Faint	..	Subcutaneous injection; this in- jection given two hours after feeding.
		24	0		
27	2.4	6	Faint	..	Subcutaneous injection.
		24	0		
May 19	2.7	4	Faint	..	Subcutaneous injection.
		24	0		
27	3.0	7½	Faint	..	Subcutaneous injection.
		24	0		
June 2	4.0	24	Faint	..	Subcutaneous injection.
8	5.0	24	Faint	..	Subcutaneous injection.
26	6.0	24	Negative	..	Subcutaneous injection.
July 2	6.0	1½	0	..	Stomach tube.
		3½	0		
		24	0		
8	7.0	2	Faint	..	Subcutaneous injection.
		24	0.34		
30	7.0	3	0	..	Stomach tube.
		24	0		
Nov. 9	7.0	24	Slight	..	Subcutaneous injection.
		24	Slight		
Dec. 10	Removed stump of the processus lienalis and adjoining part of corpus, weighing 6.3 gm.				
1915.					
Mar. 16	6.0	24	0	..	Subcutaneous injection.
June 2	3.0	3	Slight	..	Subcutaneous injection.
		8	0.69		
		12	0.82		
		24	Faint		
11	1.5	4	0	..	Subcutaneous injection.
		8½	0		
		10	0		
		24	0		
18	3.0	1	0	..	Stomach tube.
		7	0		
		9	0		
		24	0		
30	4.0	22½	0	..	Subcutaneous injection.
1916.					
Sept. 6	Removed 0.8 gm. pancreatic tissue.				
Nov. 15	4.0	2	0.26	..	Stomach tube.
		3½	0		
20		Before feeding	0	0.102	Fed 200 gm. bread.
		2	0	0.125	100 gm. lung.
		4	0.36	0.154	75 gm. glucose.
		6	0	0.149	
21		Before feeding	0	0.106	Fed 200 gm. bread.
		2	0	0.123	100 gm. lung.
		4	Faint	0.156	150 gm. glucose.
		6	Faint	0.128	
23		Before feeding	0	0.092	Fed 200 gm. bread.
		2	0	0.095	100 gm. lung.
		4	0	0.139	150 gm. glucose.
		6	0	0.130	

TABLE I.—DOG. B2-00. WEIGHT 14 KG.M. (Continued).

Date, 1916.	Glucose dosage, gm. per kgm.	Hours following injection.	Glycosuria, gm.	Plasma sugar, per cent.	Remarks.
Dec. 16	Removed 0.1 gm. of pancreatic tissue.				
30		Before feeding	0	0.085	Fed 200 gm. bread.
		2	3.45	0.345	100 gm. lung.
		4	6.46	0.455	150 gm. glucose.
		6	5.89	0.500	
1917.					
Jan. 7	..	Before feeding	0	0.125	Fed 200 gm. bread.
		2	7.13	0.400	100 gm. lung.
		4	6.68	0.400	150 gm. glucose.
		6	8.0	0.333	
Feb. 23		Before feeding	0	0.116	Fed 200 gm. bread.
		2	0.63	0.238	100 gm. lung.
		4	0.57	0.244	150 gm. glucose.
		6	0.69	0.232	

2. There are irregularities in individual tests. For example, the slight reaction with 6 gm. per kgm. on November 8, 1913, is an instance of accidental variation, and it is probable that the dog was slightly nervous during the first two tests. On January 5, 1914, there was glycosuria with 2.5 gm. per kgm. and in February and March with 1.5 gm. per kgm., while on June 26 and the ensuing March 16, after removal of more pancreatic tissue, as much as 6 gm. per kgm. was tolerated. These discrepancies with subcutaneous injection were paralleled by those found with the stomach tube administration. Possibly a real recovery of pancreatic function during the long period of time may be the reason. In general the decline of tolerance is evident as mentioned.

3. As the verge of diabetes was approached small fragments of pancreatic tissue acquired great importance. Prolonged carbohydrate-rich diet (June 30, 1915, to September 6, 1916) did not bring on diabetes. On the latter date the tolerance was perceptibly lowered by the removal of 0.8 gm. pancreatic tissue, which could never have been missed if removed from a normal animal. Diabetes was caused by the removal of only 0.1 gm. of tissue on December 16. Some influence may be attributed to the attendant inflammatory injury, but the inflammation produced by the careful removal of such a small bit of tissue is very slight.

4. Blood-sugar analyses were impossible at first but were introduced as soon as facilities permitted. They serve for little more than rough indication of the height and duration of hyperglycemia and to exclude any extraordinary slowness of absorption or variations of renal permeability. With the increasing delicacy of tests necessary at this stage, factors of this sort assumed such importance that recourse was had to intravenous tests in other animals, as described elsewhere.<sup>5</sup> The methods employed for the present animals were discontinued and for other reasons some feeding experiments were performed, which are appended for their interest in the present connection. The complication introduced by pregnancy is discussed in a subsequent paper (No. 9 of this series).

<sup>5</sup> Allen, F. M., and Wishart, Mary B.: Jour. Biol. Chem., 1920, xlii, 415.



5. These feeding experiments, from November 15 to November 23, 1916, show that although the apparent tolerance theretofore had been lowered so that glycosuria resulted from 4 gm. or less of glucose per kgm., the actual tolerance was so high that only moderate hyperglycemia and trivial glycosuria resulted from as much as 100 gm. beef lung, 200 gm. bread and 150 gm. glucose.\* As a matter of fact the attempt to produce continuous glycosuria or lowering of assimilation by the highest and most prolonged possible feeding of bread and glucose failed and the tolerance actually rose as indicated by the results in blood and urine on November 23 in comparison with the preceding days. The removal of the tiny fragment of pancreatic tissue on December 16 produced a decisive change, as shown in two ways: (1) The difference in hyperglycemia and glycosuria on the identical diet is striking and on a different plane from anything following the former operations; (2) the tendency to loss of tolerance was progressive. Slight glycosuria resulted from plain bread and soup diet, so that the diet had to be changed to beef lung. With this sparing of the function and termination of the pregnancy, improvement of assimilation was possible. Such progressive improvement was shown in the tests from December 30, 1916, to February 23, 1917, in Table I, and still more in the later ones reported in paper 3 of Series I. As there recorded the identical diet on August 9 and October 5, 1917, gave results in blood and urine practically the same as those in November, 1916. The great actual difference in condition is shown by the later history of the dog as given in the paper mentioned, for the mere prolonged continuance of a high-calory carbohydrate-free diet gradually broke down the tolerance. An agreement of physiologic and anatomic evidence thus indicates the excessive labor of an inadequate pancreas remnant in the attempt to prove equal to its task and its gradual breakdown under the strain.

This observation harmonizes with that made with the glucose tests under (2) above, where there was an apparent rise of tolerance, though the animal after removal of more pancreatic tissue must have been closer to diabetes. The conclusion must be that though some approximate information is derivable from such assimilation tests, neither the administration of glucose by stomach or subcutaneously nor the feeding of a mixed meal is necessarily decisive concerning the precise state of an animal as respects diabetes.

#### REMARKS ON DOG B2-01.

Essentially the same points are noted as in Dog B2-00. The largest subcutaneous dose which the normal animal assimilated

\* The distinction between these traces of glycosuria and the genuine limits of assimilation is illustrated further by the test of April 20, 1914, when the assimilation of 6 gm. glucose per kgm. subcutaneously was not perceptibly lowered by giving it two hours after the dog had eaten her fill of bread and soup.

without glycosuria was 7 gm. per kilo. After removal of only the splenic process, glycosuria resulted from 3 gm., but not from 2.5 gm. per kilo. After removal of the uncinat process there was glycosuria with 1.5 gm. per kilo.

TABLE II.—DOG B2-01. WEIGHT 14 KGM.

Date.	Glucose dosage, gm. per kgm.	Hours following injection	Plasma sugar, per cent.	Glycosuria, gm.	Remarks.
1913.					
Nov. 1	8.0	24	..	Slight	Subcutaneous injection; normal dog.
11	4.0	24	..	0	Subcutaneous injection; normal dog.
16	8.0	2	..	1.30	Stomach tube.
20	7.0	5	..	0	Subcutaneous injection.
20		24	..	0	
29	9.0	6	..	Slight	Subcutaneous injection.
29		24	..	0	
Dec. 6	8.0	5½	..	0.60	Subcutaneous injection.
12		24	..	Slight	
21	4.5	6	..	0	Subcutaneous injection.
21		24	..	Slight	
30	4.5	24	..	0.40	Subcutaneous injection.
1914.					
Jan. 2	3.0	24	..	0.80	Subcutaneous injection.
5	2.5	24	..	0	Subcutaneous injection.
13	4.0	1	..	Faint	Subcutaneous injection.
13		2	..	0	
13		24	..	0	
20	Removed processus uncinatus of pancreas, weighing 5.9 gm.				
Feb. 5	2.0	5	..	0.12	Subcutaneous injection.
11	1.5	4	..	0	
11		24	..	Slight	Subcutaneous injection.
Mar. 26	1.5	6	..	Faint	Subcutaneous injection.
26		24	..	0	
April 3	2.1	24	..	Faint	Subcutaneous injection.
20	2.4	6	..	Slight	Subcutaneous injection; fed bread and soup four hours before test.
27	2.4	24	..	0	Subcutaneous injection.
27		6	..	0	
27		24	..	0	
May 15	Removed splenic end of body, weighing 7 gm.				
June 1	2.0	24	..	Faint	Subcutaneous injection.
8	4.0	24	..	Faint	Subcutaneous injection.
July 9	6.0	2	..	0.72 (2.40%)	Stomach tube.
13		24	..	0	
13	4.0	2	..	Faint	Stomach tube.
17		24	..	0	
17	7.0	2	..	0.27 (2.70%)	Subcutaneous injection.
17		24	..	Slight	
Nov. 9	7.0	2	..	1.20 (5.00%)	Subcutaneous injection.
24		24	..	1.20 (2.00%)	
24	Removed pancreatic tissue weighing 1.25 gm.				
1915.					
April 30	4.0	Before feeding	0.107	0	Stomach tube.
		1	0.244	0.03 (0.25%)	
		1	0.250	0.07 (2.27%)	
		2½	0.266	0.45 (5.50%)	
		4½	..	0.92 (7.10%)	
		6	0.184	1.00 (8.30%)	
		8	0.324	0.23 (2.40%)	
		10	0.230	0.11 (0.70%)	
		12	..	Faint	
		13	0.186	Faint	
		15	0.163	Faint	
		24	0.146	0	
Sept. 29	4.0	Before feeding	0.106	0	
		14	0.256	Slight	Stomach tube.
		31	0.147	Faint	
		7	0.103	0	
1916.					
April 26	Removed pancreatic tissue weighing 0.85 gm.				
Aug. 31	Removed pancreatic tissue weighing 0.80 gm.				
Nov. 15		2	..	1.10 (6.30%)	Stomach tube.
	4.0	5½	..	1.70 (4.60%)	
		24	..	0	

The retention of actual assimilative power was shown on April 20, 1914, when the tolerance for 2.4 gm. glucose per kilo was scarcely altered (as compared with April 27) by a full meal of bread and soup four hours before the subcutaneous injection. After removal of 7 gm. additional pancreatic tissue there was a tendency to a rise of the apparent tolerance, as indicated by the trivial glycosuria from 4 gm. glucose per kilo on June 8 and July 13; but the dog was approaching the border of diabetes, as shown by the marked effect on removing 1.25 gm. tissue on November 24. Nevertheless, prolonged high starch and glucose diets were unable to produce any

TABLE III.—DOG B2-02. WEIGHT 10.5 KGM.

Date.	Glucose dosage, gm. per kgm.	Hours following injection.	Glycosuria, gm.	Remarks.
1913.				
Nov. 1	8.0	24	Slight	Subcutaneous injection; normal dog.
11	4.0	24	Slight	Subcutaneous injection.
15	8.0	1	Faint	Stomach tube.
		24	0	
20	7.0	5	0	Subcutaneous injection.
		24	0	
22	10.0	4	0	Stomach tube.
		24	0	
29	9.0	6½	0.4	Subcutaneous injection.
		24	0	
Dec. 6	8.0	5	0.2	Subcutaneous injection.
		24	Slight	
9	Removed processus uncinatus of the pancreas, weighing 6.8 gm.			
22	5.0	6	1.4	Subcutaneous injection.
		24	Slight	
30	3.5	24	Negative	Subcutaneous injection.
1914.				
Jan. 2	4.0	24	Slight	Subcutaneous injection.
13	4.0	1½	Faint	Stomach tube.
		3	0	
		24	0	
20	4.0	5½	Slight	Subcutaneous injection.
		24	0	
23	Removed processus lienalis of the pancreas, weighing 9.7 gm.			
Feb. 5	2.0	5	0.1	Subcutaneous injection.
		24	0	
11	1.5	3½	Slight	Subcutaneous injection.
		24	0	
Mar. 26	1.5	5½	0	Subcutaneous injection.
April 3	2.1	24	Doubtful	Subcutaneous injection.
20	2.4	5½	0	Subcutaneous injection; fed bread and soup three hours before injection.
		24	0	
27	3.0	6½	Faint	Subcutaneous injection.
		24	0	
May 19	3.2	4	Faint	Subcutaneous injection.
		24	Faint	
27	4.0	7	Faint	Subcutaneous injection.
		24	0	
June 2	4.0	24	Faint	Subcutaneous injection.
8	5.0	24	Faint	Subcutaneous injection.
26	6.0	24	0	Subcutaneous injection.
July 2	6.0	2½	0.6	Stomach tube.
		4	0	
		24	0	
7	4.0	3	0.9	Stomach tube.
		24	0	
13	3.0	2	0	Stomach tube.
		24	0	
17	7.0	1½	1.8	Subcutaneous injection.
		24	Faint	
Nov. 9	6.0	2	0.5	Subcutaneous injection.
		24	Slight	
Dec. 10	Removed pancreatic tissue weighing 4.75 gm.			
1915.				
June 2	3.0	24	Faint	Subcutaneous injection.
11	2.0	24	0	Subcutaneous injection.
18	3.0	24	0	Stomach tube.
30	4.0	20	0.8	Subcutaneous injection.

continued glycosuria or lowering of tolerance even with removal of 0.85 gm. additional tissue on April 26, 1916, so that diabetes actually resulted only with the removal of 0.8 gm. tissue on August 31, 1916. This operation caused no immediate striking change in the condition. A lowering of tolerance was indicated by the greater glycosuria from 4 gm. glucose per kilo on November 15 than in the last preceding test by stomach tube. But large carbohydrate meals were still almost completely assimilated and some power of regaining tolerance remained, as indicated by the lower plasma sugars on February 23, 1917, as compared with November 21, 1916. (See record in following paper.) Nevertheless, the downward tendency continued into severe diabetes, as described in the later history.

#### REMARKS ON DOG B2-02.

The observations resemble those in the two preceding dogs. The dog tolerated 7 gm. glucose per kilo subcutaneously and as much as 10 gm. per kilo by stomach tube. After the first operation the apparent tolerance subcutaneously lay between 3.5 and 4 gm. per kilo. Thus the removal of the uncinat process was as effective as the removal of the splenic process in the preceding dogs, and it may be remarked that other tests in other dogs have shown no appreciable differences in endocrine potency between different portions of the pancreas. After removal of the splenic process on January 23, 1914, the tolerance fell further so as to lie between 2 and 3 gm. per kilo, but fluctuated somewhat, and as usually the glycosuria, even with much higher dosages, was trivial. Very mild diabetes was produced by the third operation on December 10, 1914. Special mention may be made of two points in this connection: (1) No tests were performed until the following June, when the usual effort at recuperation was evidently in progress, for the apparent tolerance had risen to about 3 gm. per kgm.; (2) the operation to produce diabetes took place much earlier in this dog than in the two preceding and the diabetes occurred with fully as large a pancreas remnant. This animal therefore serves as a control to the other two, to show that the much longer carbohydrate feeding to which they were subjected was not a factor in the production of their diabetes.

The subsequent history of this dog was given in paper 2 of Series I. The evidence of the existence of diabetes was that glycosuria could be readily maintained at any time by the addition of glucose to the diet. The dog would never take glucose long without vomiting, and would eat only moderate quantities of bread, so that she remained free from glycosuria until death from rabies on September 19, 1916. The islands of Langerhans then showed slight vacuolation, so that there would evidently have been an ultimate outbreak of frank diabetes on the diet taken except for the untimely death.

TABLE IV.—DOG B2-43.

Date.	Weight, kgm.	Dosage, gm. per kgm.	Administration.	Glycosuria, gm.	Remarks.
1914.					
Feb. 4	9.2	5.0	Subcutaneous injection	Faint	Normal dog.
Mar. 26	11.1	5.0	Subcutaneous injection	Faint	
April 3	10.2	6.0	Subcutaneous injection	0	
20	11.6	7.0	Subcutaneous injection	0	
27	10.3	7.0	Subcutaneous injection	0	
May 20	Processus uncinatus stripped of peritoneal covering, vessels ligated.				
June 2	11.0	7.0	Subcutaneous injection	0	
16	Processus uncinatus removed.				
26	9.9	7.0	Subcutaneous injection	Slight	
July 9	Processus lienalis removed.				
30	10.3	1.0	Stomach tube	0	
Nov. 9	..	4.0	Subcutaneous injection	Faint	

## REMARKS ON DOG B2-43.

The dog was received in a state of fair nutrition and the original weight of 9.2 kgm. was used as the basis of reckoning dosage throughout. Thus the identical quantity of 46 gm. glucose was injected subcutaneously on February 4 at this weight, and on March 26 after the animal had been fattened to 11.1 kgm. The same trace of glycosuria occurred each time, perhaps from nervousness, for after becoming accustomed to the procedure the dog tolerated 64.4 gm. (7 gm. per kilo) without glycosuria, as she normally should do. The point here is that the changes of weight, which would be sufficient to affect the tolerance of a diabetic dog to a marked degree, had no such influence upon the assimilation of the normal animal.

On May 20 the uncinata process of the pancreas was stripped of peritoneum and the vessels and nerves entering its tip divided—in other words the operation of removal was performed except the actual removal, in order to test whether the lowering of apparent tolerance is due to actual removal of tissue or partly to trauma or nervous or circulatory disturbances. After this, 7 gm. of glucose per kilo was still tolerated without glycosuria; but after actual removal of the uncinata process, on June 16, the same dose caused slight glycosuria. Removal of the splenic process on July 9 lowered the tolerance further, so that on November 9 faint glycosuria followed the injection of 4 gm. per kilo.

## REMARKS ON DOG B2-60.

This Great Dane was fat when received and 45 kilos was assumed as the normal weight on which to reckon dosage throughout. According to paper I of Series I such a large dog would naturally have a small pancreas in proportion to the body weight, and by adding the weights of the portions of pancreas at operations and at autopsy, this particular animal was found to have 1.4 gm. of pancreas per kilo on 45 kilos weight. The tolerance is seen, nevertheless, to be fully as high as that of the normal dogs preceding.

TABLE V.—DOG B2-60.

Date.	Weight, kgm.	Dosage, gm. per kgm.	Administration.	Glycosuria, gm.	Remarks.
1914.					Normal dog.
May 19	48.6	3.0	Subcutaneous injection	0	
June 2	46.4	5.0	Subcutaneous injection	0	
8	..	6.0	Subcutaneous injection	0	
26	41.8	7.0	Subcutaneous injection	Faint	
July 8	40.0	7.0	Stomach tube	0	
13	39.2	9.0	Stomach tube	0	
Dec. 13	39.4	9.0	Subcutaneous injection	0.6	
17	Removed processus lienalis of pancreas weighing 26.6 gm.			26.6 gm.	
1915.					
June 2	38.0	4.0	Subcutaneous injection	0.52	
11	38.0	2.0	Subcutaneous injection	Faint	
18	36.4	4.0	Stomach tube	0.76	
30	39.2	4.0	Subcutaneous injection	Faint	In the first twenty-four hours after the injection 344 c.c. urine, faint glycosuria; in the second twenty-four hours after injection (fasting), 2537 c.c. urine, sugar-free.
1916.					
Feb. 17	45.0	12.0	Stomach tube	0.17	1 hour after feeding.
				1.22	2 hours after feeding.
				1.31	3 hours after feeding.
				0.25	4 hours after feeding.
				Faint	5½ hours after feeding.
Mar. 7	Removed pancreas tissue weighing 12.7 gm.				
May 8	45.0	12.0	Stomach tube	1.72	
16	Removed pancreas tissue weighing 6.81 gm.				
June 5	..	12.0	Stomach tube	1.58	4½ hours after feeding.
				0.52	6½ hours after feeding.
				0	24 hours after feeding.
20	Removed pancreas tissue weighing 9.45 gm.				
July 27	35.5	12.0	Stomach tube	7.58	5½ hours after feeding.
				9.59	20 hours after feeding.
					49.1 gm. sugar lost in feces.

The dog at first did not thrive in confinement and the weight gradually fell from 48.6 to 39.4 kilos. This difference was sufficient to raise the ratio of pancreas weight to body weight appreciably and would have increased the tolerance of a diabetic dog markedly. The complete assimilation of 9 gm. of glucose per kilo by stomach tube on July 13 and the excretion of 0.6 gm. from the same dose subcutaneously on December 13 represented about the average tolerance and indicated no rise of tolerance in the normal animal from diminution of body weight.

After removal of the splenic process of the pancreas on December 17 it will be observed that the tolerance was lowered so that faint glycosuria resulted from as little as 2 gm. of glucose per kilogram subcutaneously and an appreciable excretion from 4 gm. per kilo either subcutaneously or by stomach tube. Attention may be called incidentally to the fact that in this and numerous other experiments abundant time was allowed to pass to exclude the effects of operative trauma and assure that the alteration of tolerance was permanent.

The diminution instead of increase of diuresis in such tests was sufficiently emphasized in a former publication and therefore the urine volumes are mostly omitted from these records. But it may

be repeated that when the tolerance is lowered so that small doses, with minimal osmotic influence, maintain hyperglycemia and slight glycosuria longer than in normal animals, the rule still holds that there is marked oliguria during this period and polyuria afterward, as noticed in connection with the experiment of June 30, 1915.

At the same time, as frequently mentioned elsewhere, this marked lowering of tolerance in a non-diabetic animal is apparent and not real, in the sense that it does not represent any limitation of the actual assimilative power. This was shown by the administration of 12 gm. of glucose per kilo on February 17, 1916, when the absolute dose was 540 gm. and the total excretion 3 gm., *i. e.*, only the barest trifle more than a normal dog eliminates from the same dose. Higher dosage would have been the only requisite to obtain still higher assimilation.

Successive portions of pancreas were then removed, at first without any apparent effect upon the assimilation of the 12 gm. dose of glucose. Finally the operation of June 20, 1916, brought the animal close to the verge of diabetes. Active diabetes might in fact have been present except for the low body weight of 35 kilos at that time, due to impaired digestion and diarrhea. In previous tests the feces had been free from sugar, but on July 27 there was diarrhea, with loss of 49.1 gm. glucose. Nevertheless, the sharp change from the former condition is seen in the excretion of over 17 gm. glucose in the urine.

The dog's general health prevented continuing the tests into later stages of diabetes. The principal point of the experiment was that a large dog, with a small endowment of pancreas in proportion to body weight, possessed the average glucose tolerance of the species, and this tolerance declined no more than usual with the removal of successive portions of pancreas.

TABLE VI.—DOG B2-61.

Date.	Glucose dosage, gm. per kgm.	Weight, kgm.	Administration.	Glycosuria, gm.	Remarks.
1914.					
May 27	8.0	5.5	Subcutaneous injection	0.24	Normal dog.
June 2	6.0	5.5	Subcutaneous injection	Faint	
8	5.0	5.6	Subcutaneous injection	0	
26	7.0	6.0	Subcutaneous injection	0	
July 8	8.0	6.5	Subcutaneous injection	Faint	
13	8.0	6.1	Stomach tube	0.10	
17	9.0	6.4	Subcutaneous injection	0.30	
30	7.0	6.5	Stomach tube	Faint	
Aug. 12	8.0	6.3	Stomach tube	0	
Nov. 9	8.0	6.0	Subcutaneous injection	0.20	
13	Removed tissue weighing 11.74 gm., about two-thirds of pancreas.				
1915.					
June 2	3.0	..	Subcutaneous injection	Slight	34 hrs. after injection.
				Slight	9 hrs. after injection.
				0	22 hrs. after injection.
11	1.5	6.7	Subcutaneous injection	Faint	5 hrs. after injection.
				0	7 hrs. after injection.
15	3.0	6.9	Stomach tube	0.32	3 hrs. after feeding.
				0	10½ hrs. after feeding.
30	4.0	6.6	Subcutaneous injection	Faint	18 hrs. after injection.

## REMARKS ON DOG B2-61.

Several experiments were undertaken with much smaller animals than this, but they were not strong enough to go through the repeated tests and operations and resist distemper and other accidents. This animal was a small black mongrel, fat when received at a weight of 5.5 kilos, so that 5 kilos was assumed as the normal weight for reckoning purposes throughout. She became more obese under the conditions of cage life. According to general rules a high ratio of pancreas weight to body weight was to be anticipated and the actual finding was that this animal possessed 3.75 gm. of pancreas tissue per kilogram.

The glucose tests in the normal state indicated a slightly lower apparent tolerance both subcutaneously and by stomach tube than in Dog 260.

November 13, 1914, the two processes, representing about two-thirds of the pancreas, were removed, leaving most of the body of the gland in place. The tolerance was lowered so that faint glycosuria resulted from as little as 1.5 gm. of glucose per kilo subcutaneously on June 11, 1915.

Accordingly a small dog with a high ratio of pancreas to body weight has no higher glucose tolerance than a large dog, and there is no greater "margin of safety," as judged by the lowering of the apparent tolerance by removal of pancreatic tissue. It was already concluded from the compilation of records in paper I of Series I that there is no uniform difference, outside of the limits of error, in the proportion of pancreatic tissue which must be removed to produce diabetes in large and small dogs.

## REMARKS ON TABLE 7.

Instead of single dogs with removal of successive portions of pancreas this table is made up of different dogs possessing different portions of the gland. The "Remarks" column is occupied mostly with the fractions of pancreas remaining. Though the body weights frequently varied the original weight in each instance is used as the standard for dosage in all tests.

The normal dog No. B2-40 tolerated 10 gm. glucose per kilo subcutaneously when first received. The animal refused all food in the strange surroundings, so that from January 28 to February 3 the weight fell from 11.7 to 10.6 kilos. A smaller glucose injection was then given (6.7 gm. per kilo on the original 11.7 kilo weight), with the result of high glycosuria in a very small urine volume. A distinction must be made between this "hunger glycosuria" and the effect of simple changes of weight. A normal dog is unchanged in tolerance by changes of weight, but is subject to this transitory glycosuria or hyperglycemia on receiving carbohydrate



after long fasting or scanty diet. The true tolerance of a diabetic animal rises when the weight is reduced even by fasting, but in mild cases the sudden giving of carbohydrate after fasting or even after protein-fat diet often causes a transitory glycosuria like that of normal animals, but heavier.<sup>4</sup>

TABLE VII.

Dog No.	Date.	Weight, kgm.	Glucose dosage, gm. per kgm.	Administration.	Glycosuria, gm.	Remarks.
B2-40	Jan. 28	11.7	10.0	Subcutaneous injection	Faint	Normal dog.
	Feb. 3	10.6	6.7	Subcutaneous injection	3.8% in 7 c.c. urine	Weight lost by refusal of food.
C3-91	May 8	18.0	12.0	Stomach tube	1.1	Normal dog.
B2-59	19	41.8	3.0	Subcutaneous injection	0	Normal dog.
	June 2	40.0	5.0	Subcutaneous injection	0	
	8	..	6.0	Subcutaneous injection	0	
	26	40.0	7.0	Subcutaneous injection	Faint	
	July 7	39.1	9.0	Stomach tube	0.36	
	13	38.2	7.0	Stomach tube	0.76	
	30	42.5	5.0	Stomach tube	0	
B2-62	June 2	7.7	3.0	Subcutaneous injection	Slight	Only uncinate process present one-third to one-fourth of pancreas.
	8	7.6	2.0	Subcutaneous injection	Faint	
	26	8.3	4.0	Subcutaneous injection	0	
	July 2	..	4.0	Stomach tube	0	
	7	8.3	6.0	Stomach tube	0	
	13	8.4	7.0	Stomach tube	0	
	17	9.2	8.0	Stomach tube	Slight	
	30	9.5	8.0	Stomach tube	Slight	
	Nov. 24	Removed	pancreatic tissue weighing 0.2 gm.			
	Mar. 30	..	9.0	Subcutaneous injection	0	
	April 8	..	8.0	Stomach tube	1.25	
B2-44	June 26	22.2	6.0	Subcutaneous injection	Faint	One-fourth to one-fifth of pancreas.
	July 2	..	6.0	Stomach tube	0	
	8	22.8	7.0	Subcutaneous injection	Faint	
	17	26.9	7.0	Stomach tube	0	
	30	21.0	9.0	Stomach tube	0	
B2-38	Feb. 10	12.1	1.0	Stomach tube	Faint	One-sixth of pancreas.
B2-57	July 8	11.3	3.0	Stomach tube	2.9	One-seventh of pancreas.
	13	..	2.0	Stomach tube	2.7	
B2-26	Dec. 30	19.0	2.0	Subcutaneous	0.23	One-ninth of pancreas; non-diabetic.
	Jan. 2	..	1.0	Subcutaneous	0	
	15	..	1.2	Subcutaneous	0.15	
B2-71	June 26	13.1	3.0	Subcutaneous	0	One-ninth of pancreas, non-diabetic.
	July 8	13.3	4.0	Subcutaneous	0	
	17	13.3	6.0	Subcutaneous	Faint	
	30	13.5	4.0	Stomach tube	0	
	Aug. 12	13.0	6.0	Stomach tube	Faint	
	Nov. 19	11.9	6.0	Subcutaneous	Faint	
B2-10	Jan. 2	7.0	2.0	Subcutaneous	Faint	One-tenth of pancreas.
	5	..	1.5	Subcutaneous	0.15	Diabetes prevented first by cachexia and later by hypertrophy of pancreas remnant.
	9	..	0.9	Subcutaneous	0	
	April 3	6.0	1.2	Subcutaneous	0	
	20	7.0	1.8	Subcutaneous	Faint	
	27	6.3	1.8	Subcutaneous	Faint	
	July 7	10.7	2.0	Stomach tube	1.0	
B2-31	April 27	9.6 (11.1)	1.0	Stomach tube	1.50	One-eighth to one-ninth of pancreas, diabetic.
C3-13	June 30	13.5	4.0	Subcutaneous injection	12.7	One-eleventh of pancreas, diabetic.

Dogs C3-91 and B2-59 furnish examples of the normal tolerance in large animals, one 18 and the other above 40 kilos in weight.

Dogs B2-62 and B2-44 were examples of exceptionally high tolerance after removal of a considerable part of the pancreas. The former animal was small and the latter large, so the difference did not pertain to size. The ordinary glycosuria of such animals is so slight that it might easily be stopped by any slight cause, and the question whether the obstacle in these cases may have been a slight renal impermeability was not investigated.

Dog B2-38, possessing one-sixth of the pancreas, showed faint glycosuria from 1 gm. glucose per kilo by stomach tube.

Dog B2-57, possessing one-seventh of the pancreas, excreted 2.9 and 2.7 gm. glucose respectively from 3 and 2 gm. per kilo by stomach tube.

Dog B2-26, non-diabetic with one-ninth of the pancreas, excreted titratable quantities of glucose from 2 gm. and from 1.2 gm. per kilo, but none from 1 gm. per kilo, subcutaneously.

Dog B2-71, also non-diabetic, with one-ninth of the pancreas, showed a contrasting behavior, in that glycosuria was absent with 4 gm. and only faint with 6 gm. per kilo, both subcutaneously and by stomach tube. Attention may be called incidentally to the usual close parallelism between the results of administration subcutaneously and by stomach tube in this and other experiments.

Dog B2-10 had been left with only one-tenth of the pancreas, but was non-diabetic at the time of the tests, because illness and emaciation following operation had allowed time for successful hypertrophy of the pancreas remnant. The apparent tolerance subcutaneously lay between 1.2 and 1.8 gm. per kilo, while 2 gm. per kilo by stomach tube caused an excretion of 1 gm. of glucose.

Dog B2-31 was diabetic, with a remnant between one-eighth and one-ninth of the pancreas, but was long kept aglycosuric by a limited protein-fat diet at a reduced body weight. During this period of latent diabetes the animal, at a weight of 9.6 kilos, was given by stomach tube 11 gm. glucose, which was 1 gm. per kilo on the normal weight of 11 kilos. An excretion of 1.5 gm. glucose resulted.

Dog C3-13, diabetic, with one-eleventh of the pancreas and similarly kept free from glycosuria on protein-fat diet, received 52 gm. glucose, or 4 gm. per kilo, subcutaneously, and excreted 12.7 gm.

The last two animals illustrate diabetic characteristics, in that even in latent diabetes small doses of sugar are likely to cause an appreciable excretion, which increases markedly with the dose. As long as the diabetes is kept under control the animal evidently possesses enough of the internal pancreatic secretion to utilize the greater part of any single dose; but with repetition of doses or

any other cause of glycosuria the loss of sugar increases, even to the point where the total quantity administered is eliminated. Examples of this behavior during active diabetes have been previously given,<sup>6</sup> so that they need not be repeated here.

Any gradual character of the decline of apparent tolerance should not cause confusion as to the sharpness of the point at which the reduction of the true tolerance begins. As previously mentioned, this point may be so sharp that the removal of one-tenth of a gram of pancreatic tissue makes the difference. Before the removal of this tenth the excretion from any dosage of glucose given by stomach or subcutaneously is relatively trivial, and the maintenance of even a slight glycosuria permanently (or continuously through any long period of time) is absolutely impossible. After the removal of the tenth of a gram of tissue not only is glycosuria greater, but it can be maintained indefinitely and tends to increase. This is the condition which has always been known clinically as diabetes.

This discussion is based upon the older tests for glycosuria before the introduction of Benedict's new methods,<sup>7</sup> but the distinction is so vital as a boundary between uninterrupted health and a progressive fatal disease that it seems unlikely to be altered in principle by any improved chemical procedure.

**Discussion.** Certain quantitative deductions concerning the internal pancreatic function may be drawn from tests in the three degrees of assimilation which have long been recognized clinically.

1. *Normal Assimilation.* Here the tolerance corresponds to the average for individuals of the same species by all tests. Two factors are necessarily involved, namely, the supply of pancreatic hormone and the capacity of the body cells for storage, combustion or transformation. As the assimilation can always be overtaxed by sufficiently large doses of sugar the question may be raised as to which of these factors becomes deficient in the normal animal. It is rather surprising to find that the pancreatic element is not present in the superabundance ordinarily supposed, but that the removal of any significant fraction, such as a fourth or a third of the pancreas, causes a well-marked lowering of tolerance in the usual tests. In other words an excess of Langerhans tissue to serve as a mere "factor of safety" is not demonstrable; on the contrary there must be frequent occasions in ordinary life (such as the eating of a box of candy by a human individual), when the full power of this tissue must be exerted if the assimilation is to be strictly normal. It is therefore conceivable that the overtaking of the pancreatic function is at least one element when the normal tolerance is

<sup>6</sup> Allen, F. M.: Glycosuria and Diabetes, 1913, Chapter VI.

<sup>7</sup> Benedict, S. R., and Osterberg, E.: Jour. Biol. Chem., 1918, xxxiv, 195.

exceeded, and that if the functional capacity of the pancreas could be augmented the sugar tolerance might be raised.

2. *Lowered Tolerance.* This is understood clinically as an abnormal tendency to hyperglycemia or glycosuria from carbohydrate, but short of the point of diabetes. It is to be interpreted as a slowing of the rate of sugar utilization by the cells. There are two conceivable conditions of such slowing. (a) With any reduction of pancreatic tissue or function the cells of the body may be chronically undersupplied with the hormone. Their ordinary metabolism may or may not be affected by such deficiency, but it becomes plainly evident under conditions of strain; (b) the other alternative requires the assumption that the function of the pancreatic islands is delicately adjusted to the immediate demands of metabolism and that an increased absorption of carbohydrate requires an increased flow of their secretion. Under this conception a reduced mass of pancreatic tissue might be fully adequate for ordinary metabolism, but unable to respond perfectly to carbohydrate excess. The two alternatives are not mutually exclusive and might both be true. The latter may seem *a priori* more plausible, but some evidence favors the former idea, namely, the supply of the immediate needs of carbohydrate metabolism by pancreatic hormone stored in the tissues. This evidence consists in Verzář's<sup>8</sup> observation that the respiratory quotient falls only gradually after total pancreatectomy, and that during the first few hours intravenously injected glucose still raises the quotient; and Hédon's<sup>9</sup> assertion that diabetes comes on more quickly after removal of a subcutaneous pancreatic graft which was barely large enough to keep a dog non-diabetic, than after removal of the entire pancreas of a normal dog. If these statements, especially the latter, could be proved beyond the possibility of errors from anesthesia, trauma, differences in nutritive state, etc., they would establish (1) that the pancreatic secretion is stored in the tissues, and (2) that the store of it is greater with a normal pancreas than with a small remnant of pancreas. Evidence for the other alternative will be considered in a subsequent review.

3. *Diabetes.* This has long been identified clinically by continuous or prolonged glycosuria and hyperglycemia. In the mildest diabetes such continuance may require a maximum ingestion of carbohydrate, but nevertheless there is a sharp distinction from any non-diabetic degree of lowered tolerance, in which such a continuance is impossible. A tendency to regard this classic distinction as fictitious has been manifested by some writers who are disposed theoretically to plot the curve of falling tolerance as a diagonal straight

<sup>8</sup> Verzář, F.: *Biochem. Ztschr.*, 1912, xliv, 201; 1914, lxvi, 75. Verzář and v. Fejer, A.: *Ibid.*, 1913, liii, 140.

<sup>9</sup> Hédon, E.: *Arch. internat. de physiol.*, 1913, xiii, 4.

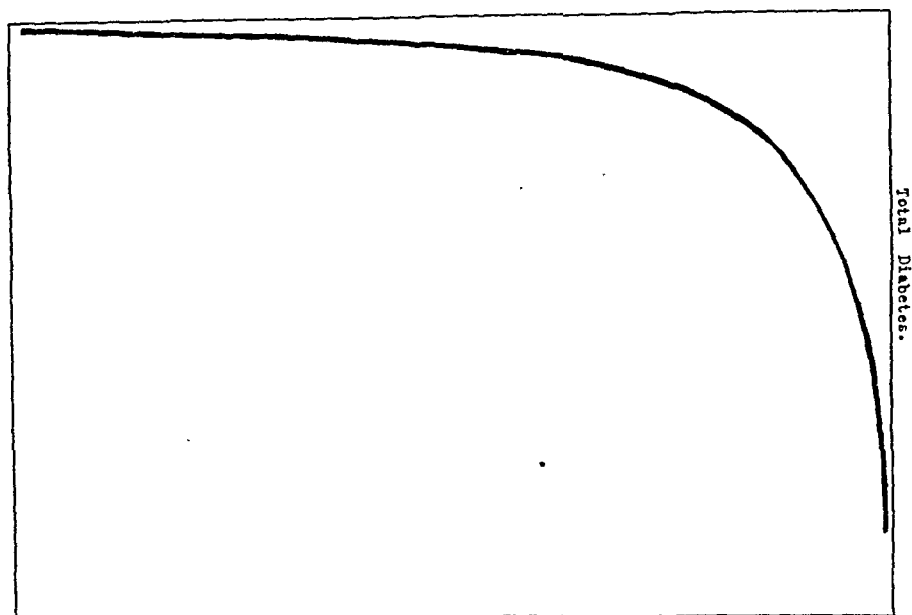
line descending from the fully normal level to total diabetes. Thus an animal which had lost one-tenth of its pancreas would be one-tenth diabetic; one that had lost one-fourth of its pancreas would be one-fourth diabetic; one that had lost nine-tenths of its pancreas would be nine-tenths diabetic, etc. Several facts refute this theoretical conception and establish the strict clinical concept of diabetes. (a) From the standpoint of gross anatomy, even though all portions of the pancreas are practically equal in potency, the curve of falling tolerance is not a straight line. The importance of a given mass of tissue increases as the total remaining mass decreases. The point is reached where the removal of 1 or 2 grams has greater effect than the removal of 5 to 10 grams in the first place, and diabetes may finally result from the removal of as little as 0.1 gm. (b) There is an important distinction in the microscopic anatomy, for hydropic degeneration of islands never occurs in the non-diabetic state no matter how low the tolerance, while it always occurs in diabetes if the island function is sufficiently overtaxed. There is a narrow border condition in which slight vacuolation of islands may be present together with glycosuria or hyperglycemia on high carbohydrate feeding, and yet the vacuolation and the diabetes both clear up permanently; but this is merely the result of hypertrophy of the remnant or subsidence of inflammation, and therefore is not a real exception to the sharpness of the boundary. This is the basis of the tendency to aggravation which is characteristic of diabetes with excessive diets and the complete harmlessness of any excess in any state of lowered tolerance short of diabetes. (c) A third distinction is found in the so-called "paradoxical law" formerly stated by the writer.<sup>10</sup> The lowering of tolerance produced by removal of the greater portion of the pancreas is apparent rather than real. Only a trivial fraction of even the largest dose of sugar is excreted; the assimilation is merely slowed somewhat and remains actually unlimited. But after removal of about seven-eighths to nine-tenths of the pancreas a difference becomes evident, suddenly or gradually according to the form of the tests. The results of single doses of sugar are not infallible and special circumstances may cause a mildly diabetic animal to show an apparently better assimilation than one that is not quite diabetic. Nevertheless, there is a striking tendency to higher and longer hyperglycemia and glycosuria, which becomes greater the longer the excessive dosage is continued. The actual quantitative excretion is considerable, and with progress to the diabetes or removal of a few small fragments of pancreas it approaches more and more closely to the total quantity administered.

It may be said therefore that the curve of lowered tolerance resulting from the removal of successive portions of pancreas

<sup>10</sup> Allen, F. M.: Glycosuria and Diabetes, 1913, p. 67.

approximates a hyperbola. (See Figure.) Starting at the vertex of this curve one limb may be traced backward as a variable approaching the normal tolerance while the other limb descends as a variable approaching the limit of total diabetes.

Normal assimilation.



Type of curve of reduction of carbohydrate assimilation by successive removal of portions of pancreas. (Ordinates, fractions of pancreas removed. Abscissæ, carbohydrate tolerance.)

**Conclusions.** 1. Dogs show an increased tendency to glycosuria from glucose given by stomach or subcutaneously when as little as a fourth or a third of the pancreas is removed. Apparently, therefore, the pancreas has little if any "margin of safety" from the standpoint of strictly normal metabolism, and there may be frequent occasions when its full endocrine function is needed for the purpose of fully normal assimilation. Quantities of sugar which exceed the normal assimilation may possibly be conceived as "overtaxing" the normal pancreatic function.

2. The internal secretory potency of different parts of the pancreas is equal, as far as such tests can determine; but the influence of a given mass of tissue increases as the total mass of remaining tissue decreases. The "margin of safety" of the pancreas with regard to diabetes is large, amounting in the dog to at least seven-eighths of the gland. The point at which diabetes begins is sharp and definite, according to three criteria: (a) An animal may be brought so close to the verge of diabetes that it is brought on by the removal of as little as 0.1 gm. additional tissue. (b) At this point a new histologic

phenomenon begins, namely, the hydropic degeneration of the islands described elsewhere, which is the basis of the characteristic aggravation of diabetes on excessive diets, while such excesses are harmless in any states of lowered tolerance short of diabetes. (c) The lowering of tolerance in any stage short of diabetes is only apparent, representing only a slight delay of assimilation while the actual capacity is unlimited, and the maintenance of continuous glycosuria through any long period of weeks or months is absolutely impossible by any quantity of sugar or any other food; but in diabetes the limit of assimilation is real and glycosuria progressively increases to the point of total excretion of the quantity administered. The curve of lowering of tolerance, with removal of successive portions of pancreas, is therefore approximately hyperbolic in form. Starting as a variable which descends by successive slight degrees below the level of normal tolerance, it turns at the vertex into a variable which approaches total diabetes as its limit.

3. Certain conceptions concerning the quantitative relations of the pancreatic hormone may be deduced as follows: It stands in some quantitative relation with the amount of carbohydrate metabolized, because a deficiency is revealed by moderate glucose dosage when only one-fourth of the pancreas is removed, and because of the above-mentioned proof that in diabetes the islands can be driven to destructive overfunction by carbohydrate excess and spared by regulation of diet. A more important quantitative relation is the minimum requirement of the body cells to prevent diabetes. When this minimum quantity of the hormone is present the organism retains its power to metabolize almost the whole of any glucose dosage that can be absorbed from the stomach or subcutaneous tissue, no matter how large or how long continued. When this minimum is reduced by only a trifle the phenomena of diabetes begin. With mild diabetes this deficit may be guarded against by restriction of carbohydrate. With more severe diabetes the total diet and body weight must be reduced. With still more severe diabetes the supply of hormone is inadequate for even the lowest metabolism and glycosuria is therefore uncontrollable even by fasting. As an example it may be assumed that a dog becomes diabetic with removal of between seven-eighths and nine-tenths of the pancreas, and in this condition requires maximal starch and sugar feeding to maintain glycosuria. Hopeless diabetes, uncontrollable by fasting, results (barring hypertrophy) when the remnant is about one-twentieth of the pancreas. The absolute difference between these fractions may be, for a fair-sized dog, perhaps 2 grams of pancreas tissue. Accordingly the difference between the demands of the highest possible carbohydrate metabolism and the demands of the lowest possible general metabolism amounts in such an animal to no more than the possible output of 2 grams of pancreatic tissue, only a small fraction of which consists of islands.

Such a calculation is of interest in animals when quantitative estimations can be made with approximate accuracy by operations. There is evidently a fallacy in the application to human patients, for it is impossible that the destruction of islands in human diabetes should always fall within the narrow limits mentioned. As a matter of fact, diabetes uncontrollable by fasting is very common in experimental animals and very rare in human cases. A possible explanation may be that one prominent feature of human cases is a functional defect which interferes with the internal secretory activity of the islands and at the same time renders them specially susceptible to damage from functional overstimulation. Such an explanation is supported by observations in other directions. One of these is the abundance of normal appearing islands in some clinical cases necessitating the assumption of a functional impairment. Another is the wide variation in the susceptibility of different human patients (especially the old and young) to degeneration of islands and corresponding decline of tolerance from dietary excess. At the same time it seems evident that a relatively small mass of normal island tissue can prevent diabetes, and the conclusion is therefore suggested that any positive means of augmenting the endocrine pancreatic function even by a little would give therapeutic results far surpassing those of the negative plan of sparing the function by diet.

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### DIAGNOSIS OF MYXEDEMA.<sup>1</sup>

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MYXEDEMA is insidious in its onset, so that for a long period of time the characteristic clinical features may be absent, or, indeed, may not appear at all. The importance, however, of recognizing this disease is shown by two facts: (1) there is a sovereign remedy for its treatment, and (2) serious physical and mental developments ensue in long-overlooked cases, eventually reaching a stage in which there is an unsatisfactory response to appropriate measures.

It has been said that the disease is easily recognized when the characteristic features are present. This view, however, does not accord with the results of my experience and previous collective investigations. For example, out of 7 typical cases which have fallen under my care, and of which I have notes, 6 had gone unrecognized. Again, of 27 cases out of a total of 55 cases collected by me from American and Canadian literature and physicians, more especially those in charge of institutions for the care of the feeble-

<sup>1</sup> Read before the American Climatological and Clinical Association, June 18, 1920.



mind, since the year 1905, 20, or 74 per cent., had been overlooked by one or more physicians. This is a sorry commentary in view of the ease with which relief is afforded after recognition. In the remaining 28 cases of my series no reference to previous diagnosis was made. Writers upon the subject of myxedema fail to stress adequately failure to diagnose the disease on the part of practitioners of medicine, including clinicians of large caliber.

The first typical case that fell under my observation had been mistaken for chronic nephritis by one of the leading medical authorities of France and another equally famous American clinician. This occurred in 1892, at which time only 1 or 2 cases had been recorded in the literature, so that allowances could be made for failure to recognize the condition. It has, however, seemed to the writer to be inexcusable to find that this disease has been commonly overlooked by practitioners in recent years. A surprisingly small number of cases of myxedema have been reported in the past, but this fact need excite no surprise in view of the foregoing statement.

It would appear that the clinical picture of myxedema, despite the excellent delineation of the characteristic symptoms to be found in classic articles on the subject and in medical text-books and systems of medicine, has not been sufficiently impressed upon the mind of the profession. This is more specially true of cases in which, and these make up the majority, some of the diagnostic features are wanting. Efforts to stimulate interest in the subject, therefore, must be regarded as both timely and important.

In order to be in a position to appreciate the numerous and varied clinical features of myxedema, it must be remembered that an infiltration of all the anatomic systems of the body occurs in this disease, leading to an increase in the general bulk of the organism. Perhaps the most characteristic sign is a firm, inelastic thickening of the skin and subcutaneous fibrous connective tissue which does not pit on pressure. The dry, swollen skin of the face obliterates more or less completely the natural facial lineaments, so that in well-marked cases the patient seems to be wearing a mask, with broad, coarse, immobile features. The same dry, firm, inelastic, myxedematous infiltration of the skin of the extremities, and notably in the supraclavicular region, is to be observed.

The mucous membranes are also infiltrated and the teeth may become loosened. Chapman has emphasized a solid appearance of the conjunctiva as an early sign. The physiognomy "is stupid, dull and phlegmatic, and simulates imbecility." The tongue, lips and nose are thickened and the voice is peculiarly monotonous and has a "leathery tone, with curious nasal explosions at short intervals during speaking."

Thought and movement are slow and heavy, and while memory is good it is slow to respond. Retardation of psychomotor action is to be regarded as being quite characteristic of the disease. In

some instances headache is complained of, and there is marked irritability of temper, while in others hallucinations and delusions, tending finally toward dementia, supervene. Trophic changes of the hair and teeth occur. Destruction of the masticating apparatus is often noted. Baldness is a common symptom, and it usually presents a special distribution, the hair of the frontal region, nape of the neck and eyebrows being first shed. Albumin is commonly found in the urine, and occasionally tube casts as well. The temperature in myxedema is more or less subnormal as a rule. The thyroid is not palpable, not only on account of its atrophy but also owing to the presence of the thickened myxedematous tissues of the neck.

The foregoing text-book description of the symptomatology of myxedema in its typical form has been given on account of my firm conviction that the profession at large has an inadequate conception of this disease. It has been well said that "disease is a thing in itself and can be recognized as readily as flowers of the field or the faces of friends when these are seen often enough." The symptoms and signs of myxedema mentioned above, however, are so characteristic as to make individual recognition perfectly easy once a single typical case has been carefully scrutinized.

As stated elsewhere by the writer: "So commonly has chronic nephritis been mistaken for this complaint outside of institutions in which careful, thorough examinations are systematically conducted as to make fresh emphasis of the importance of its diagnosis highly desirable. Notwithstanding the fact that chronic Bright's disease and myxedema present few points of contact, clinically considered, but many of distinct dissimilarity, some of which are extremely striking, the latter is constantly and sadly being confused with the former disease."<sup>2</sup>

In my statistical inquiry, which covered the period from 1905 until July, 1919, or thirteen years, complications were recorded in 43 out of 55 cases, and of these urinary features, including albuminuria, with or without the presence of tube casts, were noted in 18, or 41.5 per cent. But though albuminuria was grouped with the complication in my series it is in reality a common symptom of myxedema, and if this fact were remembered the tendency to confound this disease with chronic nephritis would be markedly lessened. Edema of the extremities and of the face and legs was reported in 8 out of the 55 cases, or 14.5 per cent. This symptom is usually due either to an associated anemia or cardiac decompensation met with in advanced cases, and until the medical profession learns that such developments sometimes take place in myxedema, wrong diagnoses

\* Myxedema and Cretinism in the United States and Canada: A Statistical Study. Contributions to Medical and Biological Research, dedicated to Sir William Osler, in Honor of His Seventieth Birthday, July 12, 1919, by his Pupils and Co-workers, i, 283.

will continue to be made. It is to be recollected that an actual nephritis may be a late accompaniment of myxedema; it then results from a generalized arteriosclerosis, or may possibly be of toxic origin. The urinary findings usually met with in chronic sclerotic nephritis (small ring of albumin, long, narrow, hyaline tube casts) are observed. It has been my good fortune to witness the disappearance of an albuminuria as the result of thyroid feeding in a number of instances of myxedema which had been regarded as cases of chronic nephritis.

To avoid mistakes in diagnosis in well-characterized cases the physical characteristics, mental condition, the slow speech and leathery tone of voice, and changes that occur in the skin and subcutaneous connective tissue, must be especially noted. Recognition of the condition is based mainly on observation of skin and mucosa, and the fact that the myxedematous infiltration of the face and legs is harsh, inelastic, stiff edema does not pit on pressure, as is true of cardiac and renal dropsy.

There are a large number of cases of myxedema which might be termed rudimentary in type, on account of the feeble development of the principal diagnostic features. Many of these cases touch certain other diseases, and especially those of endocrine origin very closely. In a case which came under my care both tuberculosis and acromegaly were associated. The myxedematous element in this case had gone unrecognized. The combined use of pituitrin and extract thyroid was followed by a remarkable degree of improvement, especially as regards the evidences of myxedema which practically disappeared, while the previous use of pituitrin alone by the attending physician had proved futile. It has been repeatedly shown by such careful observers as Schiff, Magnus-Levy and others that feeding with pituitary gland is without effect in acromegaly.

In view of the marvellous improvement in myxedema treated with thyroid extract within a few weeks the detection of the combined affection when present is a matter of much practical importance. The association of these two conditions, myxedema and acromegaly, is not infrequent, and to add to the difficulties encountered in their discrimination they present certain points of great similarity. In both the skin is dry, the subcutaneous fibrous connective tissue thickened by overgrowth, the tongue enlarged, the mucous membranes, especially of the nose, soft palate and uvula thickened; in both there is irritability of temper, slowness of the mental processes and thick, difficult speech.

Certain obvious features, however, belong to each of these diseases alone when found to be combined. For example, the general bony enlargement with separation of the condyles, enlarged joints, the severe headaches, disturbances of vision, bilateral hemianopsia are dependent on the acromegaly, while the tendency to chilling, a subnormal temperature, miniature thyroid, malar flushes and

loss of hair, as well as a peculiarly distorted physiognomy (masked facies), belong to myxedema. When these two diseases are associated in a single case the acromegalous features may overshadow the less obvious myxedematous symptoms. For example, in my case of combined acromegaly and myxedema, marked headache, strabismus, enlarged bones and joints, decidedly prognathous lower jaw, collectively pointed to the former disease, and overshadowed the fewer symptoms of myxedema. The presence of constant chilly sensations, low temperature, the malar flushes, the large myxedematous pads, however, caused me to suspect associated myxedema and led to the employment of thyroid extract, with most gratifying results.

The history of my case clearly indicated that the symptoms of acromegaly preceded those of myxedema by several years, at least. This is most probably the usual order of development when these two affections coexist, the average age at which myxedema begins being much higher than for acromegaly. On the other hand, myxedema occurring before the growth of the bones is completed causes an arrest of ossification.

In this connection Dock has called attention to the necessity of tracing out all the relations in cases of ductless-gland disease. The fact remains to be stressed that in any polyglandular syndrome which presents symptoms of myxedema, however slight, it is advisable to apply the therapeutic test. Since promising results have been recently obtained by Webster and others from roentgen-ray treatment in early acromegaly a trial of that agent might be made in combined cases in which the symptoms afford merely a suspicion of this disease.

Another endocrine disease intimately related to myxedema along metabolic lines, and not infrequently associated with it, is exophthalmic goiter. We no longer regard these two affections as being diametrically opposed to one another in their pathogenesis and symptomatology. I have elsewhere discussed this relationship and pointed out that this knowledge has been largely the result of the experimental labors of Janney and Isaacson,<sup>3</sup> who have shown that similar metabolic disturbances may be present in both hyperthyroid and hypothyroid states, and also that the blood picture in exophthalmic goiter is practically identical with that of myxedema.

Janney<sup>4</sup> proposes to substitute the term "dysfunction" of the thyroid for the less adequate hyperthyroid explanation. In many cases of exophthalmic goiter symptoms of defective thyroid function are met with, and at present writing admit of explanation, more particularly the cutaneous and osseous changes, as well as hypoglycemia. On the other hand the moderate thyroid enlargement, exophthalmos, tremor, tachycardia, psychic stimulation and

<sup>3</sup> Arch. Int. Med., August, 1918, p. 761.

<sup>4</sup> Ibid., p. 187.

increased basal metabolism depend on hyperthyroidism, or at all events toxic substances due to an abnormal amount of thyroid hormones in the blood circulation.

As elsewhere stated these cases of exophthalmic goiter with marked deficiency symptoms must be recognized and distinguished from pure myxedema. In suspected cases, the diagnosis can be materially aided by the administration of small doses of thyroid extract. Bertine<sup>5</sup> cites recent cases in which hyperthyroid and hypothyroid symptoms were combined in the same person. While it would lead too far afield to recite individual cases of associated myxedema and Graves's disease, it should be recollected that in these combined cases the symptoms of the former disease are those belonging to mild types, as a rule, hence less obvious than in the typical cases.

Several varieties of myxedema have been described. Formerly two main groups were recognized, acute and chronic, but more recently the former has been recognized as tetany. Following operations, and in exophthalmic goiter, however, myxedema may develop acutely without assignable cause. Postoperative myxedema, however, is rare, only 7 cases having been reported to date in Canada and the United States. Osler<sup>6</sup> reported a remarkable case of rapid development and fatal termination to the American Neurological Association in 1898.

There are many cases of incomplete symptomatic development in which we are justified in suspecting the disease in question and should not fail to cautiously carry out thyroid treatment with a view to confirming our suspicions. These incomplete forms have been discussed by Hertoghe,<sup>7</sup> Buschan, Pel, Osborne and others. Their course and progress vary greatly.

The symptoms in these instances of mild chronic hypothyroidism are dependent on the constant lesion of myxedema, namely, infiltration, which, however, may be slight and more or less localized. According to my observation certain features are common to all of them, *e. g.*, abnormally low temperature, an inclination to chilly sensations, a dry, often yellowish, firm, inelastic skin, disinclination to perspiration, tendency to an increase of the general bulk of the body, irritability of temper, lack of mobility of features, physiognomy dull and uninteresting and a thickened condition of the skin and mucous membranes; which is partial, often strictly circumscribed, rather than general, and most commonly affecting the lips, nose, cheeks and tongue. In isolated cases a variety of less obvious symptom groups are to be considered according to the sex and associated conditions before an assured diagnosis or a probable recognition even is possible.

<sup>5</sup> Medical Record, New York, 1916, xc, 895.

<sup>6</sup> Dock, in Modern Medicine, Osler and McCrac, iv, 895.

<sup>7</sup> Medical Record, New York, 1914.

The importance of a closer, more thorough study of these mild forms of the disease needs to be emphasized, in view of what is known of the effects of thyroid want. While our knowledge of the function of the thyroid is still incomplete it is indisputable that the cells of the body cannot attain to a perfect morphologic state when the secretion of this gland is markedly diminished. Again, as Hertoghe has pointed out, "When the thyroid supply is scarce the carrying away of cellular waste matter is slow and incomplete—mucin, fat and other principles accumulate on the spot and there form an infiltration and edema of a special kind—hard, non-depressible."

Among these mild types the following case from my records is a not rare one:

C. A. H., female, aged forty years, active housekeeper. Family history entirely negative. Had had childish diseases, including diphtheria and scarlatina, and at the age of twenty-six typhoid fever. The patient is married, has one child, aged fourteen years; menstruation has always been very painful and profuse. For three months or more before falling under my care she complained of symptoms of indigestion, cramp-like pains in the lower abdomen at frequent intervals, some distress in epigastrium immediately after food and nocturnal nausea on waking; appetite poor, flatulence, tendency to diarrhea; all symptoms aggravated during menstruation. The skin and mucous membranes exhibited a yellowish pallor, were slightly thickened, especially under the eyes, the lips and tongue, and there was some tenderness over the greater curvature of the stomach.

To these symptoms and signs were added those described above as belonging to all the various types in this group of mild forms. The use of thyroid extract was followed by a brilliant result, including normal, painless menstruation.

Another group of cases of so-called myxedema fruste, or incomplete myxedema, is characterized by irritability of temper, malar flush, apathy, neuralgias, headache, impairment of memory, tinnitus especially on lying down, slight deafness, slowness of the mental processes, undue susceptibility to cold, weak digestion, constipation, swelling of nasal mucosa, slight thickening of the skin and subcutaneous tissues often confined to certain regions of the body, early fatigue on exertion, and a moderate degree of anemia. The thyroid is usually smaller than the normal. It is to be recollected that in this variety cutaneous eruptions, such as eczema, psoriasis and urticaria, are present. In all suspicious cases I repeat it is strongly advised to make a cautious trial, with thyroid preparations as a diagnostic aid.

In one of my cases blepharitis was present and yielded to the specific remedy. In another, arthritic pains, affecting principally the knee-joints, were manifestly due to hypothyroidism; they yielded, though slowly, to small doses of thyroid. From the fore-

going examples it is clear that the specific cellular infiltrations in this disease may involve any of the body tissues, including the bones and cartilages.

In concluding it is hoped that progress resulting from continued study of these mild, imperfect forms of myxedema may tend to minimize the number of cases that escape the observation of the practitioner of medicine.

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## THE INFLUENCE OF PROTEIN FOOD ON INCREASED BLOOD-PRESSURE.<sup>1</sup>

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PROTEIN food has generally been regarded as having a definite influence on blood-pressure. A diet high in proteins has been supposed to raise blood-pressure, and *vice versa*. This principle has been widely applied in all diseases associated with hypertension, and, as a rule, a diet low in proteins, especially in meats, has been prescribed for patients exhibiting an increased arterial pressure.

It is disappointing to note on what very meager evidence the above ideas are based. Goodall<sup>2</sup> published some very convincing observations which showed that a distinct drop in blood-pressure occurred in cases of chronic interstitial nephritis on a low protein diet. Practically all other efforts in this direction, and they are very numerous, have confined themselves to general statements which either expressed an approval, or, in some instances, a disbelief, in this relation of blood-pressure to diet; however, the concrete evidence of carefully observed cases has been largely lacking.

The following blood-pressure determinations were made on patients who had been in bed for several days. This allowed the arterial tension to assume the lower level which mental and physical relaxation bring about. The manometer readings were made at approximately the same time every day. The patients were kept in bed continuously during this study. The long period over which some of the observations were carried out serves as a control for the fluctuations that may occur in the level of blood-pressure of individuals suffering with hypertension. During the periods of low-protein feeding the diets did not contain meat, meat products

<sup>1</sup> Read before the Association of American Physicians, May 4, 1920. The cases reported in this paper were observed at the Medical Clinic of the Johns Hopkins Hospital.

<sup>2</sup> Boston Med. and Surg. Jour., 1913, clxviii, 760.

(such as soups or gravies) or fish. These foods were taken in considerable amounts on the days of high protein feeding.

CASES 1, 2 and 3.—Neither a high nor a low protein diet have any remarkable effect upon the blood-pressure in a few days.

TABLE I.—Blood-pressure Observations on Case 1. (Chronic diffuse nephritis of slight degree.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c. Total N. P. N.	Diet.	
	Systolic.	Diastolic.		Protein, gm.	Character.
1 . . . . .	164	110	31.8	20	Low protein.
2 . . . . .	165	108	....	19	
3 . . . . .	162	106	....	20	
4 . . . . .	152	110	29.7	21	
5 . . . . .	156	96	....	166	High protein.
6 . . . . .	160	96	....	196	
7 . . . . .	175	110	....	201	
8 . . . . .	170	106	....	136	
9 . . . . .	150	106	37.0	150	

TABLE II.—Blood-pressure Observations on Case 2. (Female, aged fifty-six years, arteriosclerotic kidney of moderate degree; the urine contains a trace of albumin and a few fine granular casts; the urinary specific gravity varies between 1005 and 1015; 45 per cent. of phenolsulphonephthalein is excreted in two hours and ten minutes.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c. Total N. P. N.	Diet.	
	Systolic.	Diastolic.		Protein, gm.	Character.
1 . . . . .	175	118	21.2	11	Low protein.
2 . . . . .	155	114	....	10	
3 . . . . .	170	122	....	12	
4 . . . . .	156	120	25.4	10	
5 . . . . .	155	100	....	114	High protein.
6 . . . . .	166	104	....	107	
7 . . . . .	154	100	....	119	
8 . . . . .	184	70	....	131	
9 . . . . .	160	115	33.9	123	

TABLE III.—Blood-pressure Observations on Case 3. (Male, aged sixty-three years, essential hypertension; renal function normal.)

Day.	Blood-pressure.		Diet.	
	Systolic.	Diastolic.	Total calories.	Protein, gm.
1 . . . . .	204	124	2061	126
2 . . . . .	205	120	2055	125
3 . . . . .	...	...	2056	124
4 . . . . .	185	120	2063	126
5 . . . . .	218	138	2063	126
6 . . . . .	189	117	2212	78
7 . . . . .	166	110	2060	125
8 . . . . .	205	125	2061	126

CASE 4.—There is no notable change in the level of the arterial pressure on a high or a restricted protein intake, while the total number of calories is maintained at a constant level.



TABLE IV.—Blood-pressure Observations on Case 4. (Male, aged sixty-seven years. Secondary contracted kidney; at times a trace of albumin and a few hyalin and granular casts; a phthalein excretion of 25 per cent. in two hours and ten minutes; urea nitrogen, 34 mg. per 100 c.c. of blood; moderate arteriosclerosis.)

Day.	Blood-pressure.		Diet.		
	Systolic.	Diastolic.	Protein, gm.	Total calories.	Character.
1	190	120	91 (28) <sup>3</sup>	2344	Normal diet.
2	175	105	86 (19)	2498	
3	195	115	80 (28)	2501	High protein.
4	190	110	125 (69)	2065	
5	178	112	125 (74)	2065	
6	194	120	125 (75)	2065	
7	183	125	125 (76)	2065	
8	188	115	125 (76)	2065	
9	187	119	125 (69)	2065	
10	190	116	125 (79)	2065	
11	170	103	125 (64)	2065	
12	175	105	125 (80)	2065	
13	195	108	125 (78)	2065	Restricted protein.
14	182	104	125 (68)	2065	
15	185	113	125 (76)	2065	
16	187	107	125 (80)	2065	
17	175	115	125 (72)	2065	
18	194	109	50 (18)	2065	
19	181	109	50 (16)	2065	
20	178	100	50 (29)	2065	
21	173	103	50 (18)	2065	
22	209	114	50 (29)	2065	
23	178	105	50 (16)	2065	
24	203	115	50 (11)	2065	
25	188	117	50 (16)	2065	
26	173	106	50 (16)	2065	
27	183	110	50 (16)	2065	
28	182	110	50 (16)	2065	
29	182	110	50 (17)	2065	
30	190	115	50 (14)	2065	
31	206	125	50 (17)	2065	
32	190	125	50 (14)	2065	
33	210	120	50 (20)	2065	
34	195	115	50 (19)	2065	
35	201	115	50 (31)	2065	
36	185	115	50 (21)	2065	
37	205	110	50 (13)	2065	
38	205	105	50 (29)	2065	
39	202	112	50 (18)	2065	

<sup>3</sup> Figures in parentheses are the quantity of protein from meat or fish.

CASES 5 and 6.—The low protein diet is effective in producing a diminution in the blood urea nitrogen, but the blood-pressure remains unchanged.

TABLE V.—Blood-pressure Observations on Case 5. (Male, aged thirty-five years; secondary contracted kidney; albuminuria moderate; a few hyalin and fine granular casts; phthalein excretion, 21 per cent., in two hours and ten minutes; low fixed specific gravity of urine; albuminuric retinitis.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
1	210	140	61	97	..	Low protein.
2	...	...	..	..	15	
3	210	140	..	..	18	
4	...	...	41	70	20	
5	215	140	..	..	43	100 gm. turkey added one day only.
6	...	...	..	..	53	
7	210	135	..	..	28	
8	...	...	..	..	29	
9	...	...	..	..	25	Bread $\pm$ 300 gm. added. " " " " " " " " " " " " " "
10	218	140	24	38	26	
11	...	...	..	..	25	
12	...	...	..	..	31	
13	210	145	..	..	44	
14	...	...	..	..	33	
15	220	145	..	..	29	
16	...	...	..	...	26	
17	210	140	..	..	24	
18	...	...	..	..	33	
19	213	145	15	22	28	
20	...	...	..	..	21	
21	200	139	..	32	65	
22	...	...	..	..	54	
23	...	...	..	..	53	
24	224	145	21	32	66	
25	...	...	..	..	68	
26	238	148	..	..	29	
27	213	140	..	..	59	

TABLE VI.—Blood-pressure Observations on Case 6. (Male, aged thirty-two years; an advanced case of arteriosclerotic kidney; the urine contains a trace of albumin and a few granular casts; the specific gravity is absolutely fixed at a level of 1010; only a trace of phthalein is excreted in two hours and ten minutes; Ambard's constant is 0.77; the blood-urea nitrogen is given in the table.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total calories.	Protein, gm.	Character.
1	191	122	105	850	17	Low protein.
2	196	124	...	1571	15	
3	182	116	...	1626	16	
4	180	120	...	1721	16	
5	185	123	...	1755	19	
6	194	119	...	1778	20	
7	200	125	...	1838	20	
8	212	125	...	1687	20	
9	192	115	66	2396	82	

CASE 7.—A diet low or restricted in proteins is not accompanied by a drop in blood-pressure. An increase of the caloric value of the food results in no changes in the arterial tension.

TABLE VII.—Blood-pressure Observations on Case 7. (Male, aged forty-six years; secondary contracted kidney, with considerable impairment of renal function; phthalein, 26 per cent., in two hours and ten minutes; blood-urea nitrogen, after low protein diet, 27 mg. in 100 c.c.; Ambard's constant, 0.144; albuminuria, about 1 gm. per liter; many hyalin and granular casts.)

Day.	Blood-pressure.		Total calories.	Protein, gm.	Character.	Diet.			
	Systolic.	Diastolic.				Additions to diet.			
						Eggs, No.	Oatmeal, gm.	Milk, cream, c.c.	Meat, gm.
1 . .	230	160	..	..	Ward diet				
2 . .	219	155							
3 . .	215	160							
4 . .	219	161	..	..	Low protein				
5 . .	235	158							
6 . .	232	160							
7 . .	230	140							
8 . .	230	150	1676	22					
9 . .	234	160	1722	17					
10 . .	232	155	1937	22					
11 . .	232	153	2038	25					
12 . .	221	138	2116	34					
13 . .	229	155	2274	36					
14 . .	234	144	2136	38					
15 . .	242	145	2299	47	....	3			
16 . .	220	137	2302	49	....	3			
17 . .	215	140	2300	48	....	3			
18 . .	217	142	2110	39	....	2			
19 . .	235	155	1552	17	Calories				
20 . .	242	154	1513	17	Lowered				
21 . .	222	153	1604	20					
22 . .	231	145	1644	19					
23 . .	224	145	1841	20					
24 . .	228	145	1570	19					
25 . .	224	155	2037	28	Calories				
26 . .	228	145	2496	36	Raised				
27 . .	218	135	2410	38					
28 . .	220	138	2509	47	....	..	400	245	
29 . .	229	150	2641	48	....	..	400	290	
30 . .	232	145	2601	48	....	..	400	320	
31 . .	218	145	2781	51	....	..	400	260	
32 . .	214	147	2504	50	....	..	400	260	
33 . .	220	145	2619	50	....	..	400	290	
34 . .	224	145	2616	50	....	..	400	230	
35 . .	218	143	2402	47	....	..	400	260	
36 . .	220	142	2511	59	....	..	400	230	50
37 . .	220	145	2669	63	....	..	400	280	50
38 . .	224	152	2767	63	....	..	400	180	50
39 . .	224	138	2761	74	....	..	400	280	100
40 . .	218	138	2772	77	....	..	400	230	100
41 . .	225	135	2718	65	....	..	400	230	50
42 . .	230	148	2873	70	....	..	400	130	50
43 . .	228	144	3026	73	....	..	400	310	100
44 . .	214	145	2719	74	....	..	400	230	100
45 . .	...	...	2819	75	....	..	200	260	100
46 . .	232	145	2361	75	....	..	200	335	125
47 . .	230	142	2819	75	....	..	200	260	150

CASE 8.—There is a tendency for a diminution of the blood-pressure with a diet very low in protein and low in caloric value.

TABLE VIII.—Blood-pressure Observations on Case 8. (Female, aged forty-one years; secondary contracted kidney, with marked impairment of renal function; phthalein, 10 per cent. in two hours and ten minutes; blood-urea nitrogen, 45 mg. in 100 c.c.; specific gravity of the urine fixed at a level of 1010; marked albuminuria and many hyalin and granular casts.)

Day.	Blood-pressure.		Diet.		Character.
	Systolic.	Diastolic.	Protein, gm.	Total calories.	
1 . . . . .	188	108	10	489	Low protein.
2 . . . . .	...	...	14	972	
3 . . . . .	190	110	14	898	
4 . . . . .	190	109	10	888	
5 . . . . .	175	100	11	664	
6 . . . . .	165	80	9	713	
7 . . . . .	165	80	9	897	
8 . . . . .	160	85	6	583	
9 . . . . .	155	84	9	766	
10 . . . . .	163	90	8	688	
11 . . . . .	150	85	8	623	
12 . . . . .	160	85	8	538	
13 . . . . .	164	95	8	714	
14 . . . . .	...	...	8	561	
15 . . . . .	185	115	7	608	

CASE 9.—A distinct drop in the blood-pressure occurs with the initial period of low protein diet. The original height of the blood-pressure is promptly resumed when 250 gm. of meat are added to the diet. When the meat is discontinued and the low protein diet substituted the blood-pressure does not fall to the previous level which the first period of low protein feeding produced.

TABLE IX.—Blood-pressure Observations on Case 9. (Male, aged twenty-five years; secondary contracted kidney, with marked impairment of renal function; phthalein, 10 per cent. in two hours and ten minutes; blood-urea nitrogen as in the table; Ambard's constant, 0.63; albuminuria marked; hyaline and granular casts.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
1 . . . . .	165	120	..	...	..	"Ward, light."
2 . . . . .	165	120				
3 . . . . .	160	90				
4 . . . . .	166	100				
5 . . . . .	165	103				
6 . . . . .	160	100	99	125		Low protein.
7 . . . . .	163	100	..	...	5	
8 . . . . .	165	100	..	...	7	
9 . . . . .	160	105	..	...	4	
10 . . . . .	150	98	..	...	6	
11 . . . . .	146	97	..	...	8	
12 . . . . .	145	95	..	...	10	
13 . . . . .	125	88	126	145	9	
14 . . . . .	125	85	..	...	8	
15 . . . . .	125	90	..	...	10	
16 . . . . .	125	90	..	...	9	
17 . . . . .	130	80	..	...	11	
18 . . . . .	125	85	..	...	10	
19 . . . . .	125	85	..	...	9	
20 . . . . .	127	82	103	123	9	
21 . . . . .	130	85	..	...	11	

TABLE IX (Continued).

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
22	135	88	..	...	13	
23	135	88	..	...	15	
24	145	98	..	...	15	
25	145	103	..	...	12	
26	160	103	..	...	14	
27	165	112	..	...	13	
28	150	103	49	66	17	
29	140	95	..	...	10	
30	137	88	..	...	16	
31	135	90	..	...	12	
32	140	97	..	...	13	
33	143	98	..	...	15	
34	145	98	32	...	13	
35	147	100	..	...	68	250 gm. meat added
36	155	105	..	...	75	
37	169	122	..	...	52	
38	170	120	64	...	72	
39	170	120	..	...	73	
40	170	120	..	...	52	
41	170	120	..	...	52	
42	168	115	..	...	84	
43	169	118	..	...	47	
44	167	116	..	...	26	
45	150	105	.63	95	53	
46	155	107	..	...	75	
47	163	107	..	...	74	
48	170	110	..	...	71	
49	170	117	..	...	16	Meat discon- tinued.
50	170	113	..	...	16	
51	168	110	..	...	14	
52	170	115	55	79	17	
53	165	112	..	...	10	
54	169	122	..	...	18	
55	172	117	..	...	17	
56	168	120	..	...	18	
57	168	120	..	...	16	
58	173	117	..	...	18	
59	170	115	30	41	17	
60	170	116	..	...	19	
61	180	120	..	...	20	
62	...	...	..	...	21	
63	...	...	..	...	16	
64	175	120	..	...	14	
65	182	116	23	32	14	
66	180	116	..	...	18	
67	182	120	26	36	24	

**Conclusions.**—From these observations it would appear that it is exceptional for a low protein diet to diminish the blood-pressure or a high protein diet to raise it. Case 9, however, shows that this may occur. This patient was extremely ill, as the great impairment of renal function indicates, and was necessarily maintained in a state of undernutrition, since any attempts to increase the food resulted in uremic symptoms. However, even in this case a

second period of low protein feeding failed to bring the blood-pressure to the low level previously obtained.

The diminution of the waste products in the blood, as indicated by a lowering of the blood urea nitrogen, was without effect upon the blood-pressure. Changes in the caloric value of the diet, for a short time at least, did not influence the blood-pressure.

*Discussion.* The basis upon which the impression that a low protein diet reduces blood-pressure rests may possibly be found in the recent report of F. G. Benedict<sup>4</sup> and his collaborators. These investigators demonstrated that by underfeeding the blood-pressure of healthy, young, male adults could be distinctly reduced. This change was accompanied by various other phenomena, among them a secondary anemia. These facts furnish a suggestion as to the therapeutic application of diet to hypertension. A subcaloric mixed diet may be continued for a considerable period, probably with beneficial effect. If the health and strength of the patient are to be maintained it is advisable to regulate the amount of the diet according to the hemoglobin content of the blood. The hemoglobin percentage should not fall below 85 per cent. From the data given in the present communication it is evident that in most instances a low protein diet continued for a period of a few weeks is without effect upon the blood-pressure of cases of hypertension.

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## THE MANAGEMENT OF THE HEART IN PNEUMONIA.

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MUCH of the experimental work which has been done in the past few years has tended to indicate that the importance generally attributed to the heart in the acute infections may have been overestimated in the past and that the causes of death in this disease lie largely outside the heart and that therefore treatment of whatever kind directed toward the heart may be of no avail.

This tendency appears to have followed largely after the conclusions of MacCallum, who found in experimental animals evidence tending to the impression that the heart is not essentially diseased in diphtheria.<sup>5</sup> MacCallum's conclusions were soon applied, at

<sup>4</sup> Human Vitality and Efficiency under Prolonged Restricted Diet, Carnegie Institution of Washington, Publication No. 280, 1919.

least in part, to pneumonia. The authors have, however, as yet to find any large list of carefully recorded microscopic examinations from a large number of cases which conclusively overthrow the old opinion of pathologists that in most of the acute infections an acute parenchymatous degeneration of the heart muscle is caused which, while of course not of a sufficient degree to immediately wipe out the possibility of contraction on the part of the heart muscle, so compromises this power that the organ is no longer able to "carry on" under the additional load above the normal which exists in most acute infectious diseases, and particularly in pneumonia.

The tendency of this viewpoint, which has naturally been developed chiefly by physiologists, pathologists, or at least men with but little actual bedside experience, has been toward a therapeutic nihilism which is becoming a very serious matter in the training of our young clinicians. We feel that the time has now come when this matter should be frankly considered more, or rather again, from the standpoint of the active clinician whose actual opportunity for observation in these matters is greater and whose interests are more from the standpoint of the humanitarian. Few men of large clinical experience are therapeutic nihilists, and it is a most unfortunate fact that so very many young practitioners are now being instructed largely along lines which cause them to go out into practice with the idea that the employment of drugs is useless, unscientific and almost unethical.

This tendency has been one of specially grave importance in the clinical management of pneumonia; this has appeared particularly to the authors who, during the past five years, have been thrown into intimate contact with very many young physicians in their ideas of this disease and its treatment.

We feel that the time is not only ripe but pressing when the clinician should have his say in regard to these matters and because he is no pessimist and because his experimental animals are human beings whom he is attempting to heal or render more comfortable is no argument that therefore his conclusions or viewpoints are unscientific or untenable.

We appear therefore with a brief for a therapy directed to aid the heart in pneumonia. This need we believe has not been sufficiently emphasized in modern teaching, or where it has been touched upon in treatment, the reference has often been buried in a mass of detailed recommendations, largely of what we believe to be of lesser importance, to such an extent that the position of the heart as of premier or almost single importance in the successful management of this disease has been, at times, lost sight of.

Few pathologists to our knowledge, even among those who fail to find sufficient evidence upon which to indict the heart for most fatal endings in pneumonia, but still admit the presence of acute degenerative changes in the heart muscle in this disease, though

usually of early and therefore not pronounced degree. This important agreement in observation interests us particularly, because it shows but a difference in degree of acknowledged responsibility of the heart in pneumonia between clinicians and other observers. W. W. Hamburger reported at the last meeting of the Association of American Physicians a group of carefully worked-up cases which fully substantiates our conclusions in this respect.

In March, 1919, it was the privilege of one of us to analyze, in association with Dr. Clarke, pathologist of the Ancon Hospital, five thousand protocols of cases dying of pneumonia in the A. E. F. In the study of this large material, which had been collected by all the pathologists then working with the army in France, certain points stood out which confirmed observations and suspicions in regard to the disease which had been formed from our previous much more limited but intimate personal pathologic and clinical experience with pneumonia. It is true that most of the cases which formed the particular basis of the Dijon study were instances of influenzal or postinfluenzal pneumonia, and that in several features these differed from what has been considered as typical of the usual broncho- and lobar types of pneumonia, but however the etiologic factors may have differed from the customary, the mechanical features of the disease and presumably the chemical also, are practically alike if not entirely identical.

One of the most outstanding and striking facts in connection with pneumonia is that fatal cases terminate almost invariably with what appears clinically as a cardiac death. In but very few instances from the whole material collected at Dijon could any other conclusion be drawn. Cases in which the involvement of the lung parenchyma was sufficient to justify the conclusion that death had ensued as the result of pulmonary deficiency were very few in number. This applied alike to both lobar and to the bronchial type of cases, and indeed, insofar as the heart itself is concerned it seems to make but little difference as to the type of the anatomic distribution of the consolidation. In general this seems also to hold true when one attempts to take into consideration the difficult question of the organism apparently responsible for the pulmonary disease in any instance.

None the less, degeneration of the kidney, very rarely sufficient to cause death was found in 712 instances of the 1651 cases investigated by Dr. Clarke. The less frequent complications of pneumonia, meningitis, sepsis, sinusitis, septic arthritis and so on are probable factors of serious consideration, but rarely when one studies the disease solely from its immediate terminal factors. Pneumonia from the standpoint of fatality, pathologically as well as clinically, may then be considered as a two-system disease; of the respiratory and the circulatory organs. When we consider the immediate termination alone it is practically always circulatory. The whole



battle in pneumonia, we would say, centers about two systems, the pulmonary and the circulatory. In but few cases is the termination other than through an apparent cardiac failure.

Analysis of these protocols showed us that the generally accepted clinical assumption is correct, namely, that the predominating cardiac lesion in pneumonia is an inflammation or degeneration of the heart muscle. It was present thus in 748 out of 1651 protocols.

We can readily see how the single-minded viewpoint of the pathologist might fail to see in many of the lesser degrees of degenerative lesions a sufficient cause for failure of the damaged organ. He, as a rule, is not given to evaluating, as the clinician is wont to do, the narrow margin of safety in the reserve physiology of the heart or the measure of added strain the organ may be called upon to undertake. As MacKenzie points out, heart failure is but exhaustion of the reserve force, and death appears immediately with exhaustion of the rest force. "It cannot be too strongly insisted upon that that process which we recognize as natural in a healthy individual is identical with the process occurring in an individual having some defect, whether the defect is due to disease of the heart itself or to other factors which embarrass the heart in its work."

In arriving at conclusions regarding the responsibility of right-heart failure for collapse and death in pneumonia the state of the heart muscle must be considered in connection with its inherent very low physiologic force (reserve and rest) as well as with the amount of unusual demand put upon this tissue during the course of pneumonia.

A fair measure of the normal reserve and rest force in the right heart may be arrived at from a consideration of the physiology of the lesser circulation and also the influence of peripheral strain which is the measure of left-heart strain on the pulmonary circulation. Wiggers's<sup>5</sup> work shows that the maximal pressure in the pulmonary system is 31.3 mm. Hg, the minimal 5.9 mm. Hg, the mean 19 mm. Hg, and the mechanical action of the respiratory movements contributes approximately 32 to 40 per cent. to the height of the maximal pressure and depresses the minimal pressure 10 to 20 per cent. "It appears that a change in total peripheral resistance is practically without influence on the pulmonary circuit when the change opposes the cardiac output in its effect."

From these facts the inference is justifiable that the reserve and rest force of the right heart is very small and its capacity for work in health or disease cannot be evaluated in terms of the left heart capacity. Clinically, unfortunately, the cardiac possibilities are usually taken as of the left heart. This is particularly untrue in pneumonia.

The amount of initial strain on the pulmonary circulation in pneumonia is indicated in part by the work of Gross<sup>13</sup> in a radiographic study of injected lungs from cases dying of pneumonia.

He demonstrated that varying degrees of vascular obliteration occur depending on the stage of pulmonary consolidation. In the stage of red hepatization there is a moderate preservation of the circulation, but there exist spaces in which vessels cannot be injected and even those injected are narrowed and compressed. In gray hepatization there is a general lack of injection and only the compressed large branches appear patent. These large branches ended abruptly and the whole area of gray hepatization presented a strikingly anemic appearance. The pathologic physiology of the obstructed pulmonary circulation lesions shown by Cross may be seen in such studies as those of Wiggers<sup>3</sup> with neutral oil injections: "*Small amounts may be without effect on the mean arterial pressure, but the pressure curves recorded from the right\* ventricle showed typical signs that the right ventricle was contracting against an increased resistance.*" Larger doses produced a fall of mean arterial pressure; the pressure in the pulmonary artery increased and the effective venous pressure also was markedly increased.

These facts substantiate, we believe, the clinically accepted fact that every case of pneumonia begins with a strain on the right heart, and that this strain, in the light of known facts of the physiologic reserve in the part, is in amount that which justifies the conclusion that the *paramount factor in prognosis of all forms of pneumonia lies here, and that upon the ability of the right heart to resist the mechanical and toxic effects of the disease, mostly depends the fate of the patient.*

It would seem that much of the skepticism about the responsibility of the right heart insufficiency in pneumonia is attributable to the absence in many cases of outspoken cardiac distress. Stasis of any extent is an expression of a considerably increased blood mass which is contrary to Sandelowsky's<sup>4</sup> finding of a concentration of the blood in pneumonia. The already narrowed pulmonary circulation does not admit of total insufficiency to the point of extensive stasis without a sharp picture of collapse. Right-heart dilatation, unless immediately and vigorously treated is rapidly fatal, and it occurs before extensive gross or microscopic lesions of the heart have time to develop. The point we wish to make is that in pneumonia we are dealing with an acute initial maximal right heart strain plus a sharp narrowing of the factor of reserve in the pulmonary circulation superadded to a degenerated condition of the muscle consequent on the toxemia of the infection. Relative lesser circulatory insufficiency is accompanied by a severe general clinical picture bordering on or actual collapse, and diagnosis must therefore be in large part by inference and treatment to be of use, must be instituted to aid the work of the right heart from the beginning and in anticipation of its failure. This can be usually accomplished by the early and intelligent exhibition of digitalis.

\* Italics ours.

We are, of course, fully aware that many instances of left heart failure occur in pneumonia. Its signs and symptoms are obvious and so striking that they can hardly escape the observation of any careful physician. We do not discuss them extensively here because of this fact and the still more important one that the treatment for the one condition suffices equally well for the other.

Believing, as we do, that heart failure in pneumonia is usually a matter of right-heart insufficiency the clinician must not then look for signs of left-heart disease or incompetence, but for the far more difficult signs and symptoms of early right-heart disease.

Up to within a few hours, or even moments of a right-heart failure, the sounds of the left heart may remain normal, the pulse-pressure may be within normal limits and the peripheral circulation well maintained.

What then are the signs and symptoms of impending right-heart failure? They may be entirely absent up to the very moment of failure, due to the very narrow margin of reserve force which the right heart possesses in health and much more so when it is diseased.

The signs of structural change in the heart, difficult as they may be to make out, may be seen in an increased diameter to the percussion surface. Failure to find this does not underwrite a competent heart. Fluoroscopy, however, will show early a right auricular dilatation. Of the patient's sensations, precordial distress, a sense of weakness and air hunger are important and significant signs. Jugular engorgement, indicating positive venous pressure, is an important sign, but this sign is also subject to intrathoracic pressure factors in the absence of true stasis. Among the most frequent signs of right-heart failure are unexplained increase in cyanosis, dyspnea and the appearance of substernal discomfort and edema of the lungs. A weakened second pulmonic tone is an important auscultatory sign. One must not expect peripheral edema and general cyanosis as in the usual signs of left heart incompetency.

We believe that small doses of digitalis at the outset of the infection enable the right heart to realize in the presence of an initial increased pulmonary pressure, a compensatory circulatory adjustment. Through this compensation at the onset the right heart in most instances is able to maintain an equilibrium. This appears to be so, as the greater number of cases of pneumonia survive throughout a considerable period of this and added strain. But we believe that every additional millimeter of strain added by factors other than those incidental to the vessels involved in the consolidation, counts—and counts very materially. In the discussion of these added factors the analysis of anoxemia offers itself as a means to that end.

From Hoover's work<sup>10</sup> we see that a fixed factor in oxygen unsaturation is a part of every case of pneumonic consolidation; that

is, the venous blood which flows through the involved area is returned to the aorta unchanged. This amount of anoxemia is a fixed factor and remains so until either there occurs obliteration of the vessels or resolution. Additional causes of increase in the unsaturation lies in shallow breathing, immobilization of the diaphragm and thorax and asynchronism—conditions which, in addition to their encroachment on the vital capacity of the lung, materially add to the right heart strain. The method of choice in combating these complications may be the oral insufflation apparatus of Meltzer,<sup>12</sup> which may supply a long-felt want in conditions requiring full artificial respiration. The subject of moisture in pneumonia is one intimately connected, we believe, with right-heart strain. In connecting moisture in the lung with right-heart strain, Mackenzie seems to stand almost alone. This rests upon the fact established originally by Welch that the cause of the high capillary pressure in the lung which explains the filtration, lies in a weakening of the left heart in the presence of a competent right heart. While this is true the essential factor behind the filtration is increased pulmonary pressure. Starling found that raising the pressure to 50 mm. for a few minutes was sufficient to cause an increase of loss by filtration of 10 to 15 per cent. of the blood volume. It appears therefore that fluctuations of pulmonary pressure in high values, even in the presence of a competent left heart, readily explain the appearance of moisture.

Bolton, working in Starling's laboratory,<sup>8</sup> has shown that stagnation of the blood alone, without either plethora or raised capillary pressure, may suffice to produce edema. It would seem, then, that regarding edema as an expression of variations in pulmonary pressure and as an indication for the use of means to relieve pressure increase is a rational inference. Moisture is a potent cause of increase in the oxygen unsaturation, and it is in such a state that the use of oxygen insufflation may be expected to materially reduce the cyanosis.

There are yet other very important problems which appear in the management of cases of pneumonia, which are important because of their relation to cardiac integrity. One of the very important of these is that of physical strain. Every clinician has noticed the very serious consequences which frequently follow when the patient is allowed to move about the bed at will, when he is allowed to sit up, and so on. Do all of us appreciate the very considerable physical strain to which we may subject the diseased heart when we insist on a complete and carefully detailed examination of our patient? If, as we have seen done, pneumonia cases are required to sit up in bed for demonstration to a class of students or to gratify the curiosity of the clinician at frequent intervals, the strain and exhaustion of our patient is very great. In instances in which question as to this statement has been raised we have asked the "doubting Thomas"

to count the pulse and to note the quality and rhythm of the patient's heart action before and after his examination and to particularly note increased dyspnea and cyanosis. For the sake of the heart the pneumonia case should be disturbed as little as possible. Meddling hydrotherapeutic measures, too frequent and too minute and too altogether careless examinations of the patient, have in our experience several times provoked an acute dilatation of the heart and exitus. We cannot insist too explicitly that the handling of the pneumonia patient must be as infrequent and as gentle as possible, all chiefly because of the heart. We have found, as probably have most other clinicians, that the use of the roentgen ray and fluoroscope is of tremendous assistance in the satisfactory study of cases of pneumonia, especially in the detection of complications, including sometimes dangerous degrees of right-heart dilatation. We found, moreover, that unless it was possible for the necessary manipulations to be carried out by carefully trained and thoroughly supervised teams of nurses and orderlies it was safer to forego the benefits of the method. Joslin, at Camp Devens Base Hospital in 1917 and 1918, permitted specially trained teams only to handle his cases and we very profitably copied his method at Camp Upton. When the pulse-rate was accelerated as a result of examination, in spite of its great utility, such examination was discontinued in all grave cases. Because of the heart, cases of pneumonia must be kept quiet and examined only as often as absolutely necessary, and then with great gentleness and as expeditiously as possible. Protection from mental strain is as important as that of physical strain in these cases. This is particularly so in excitable or irritable individuals, too much bustle in the ward, an excitable or talkative nurse or orderly, solicitous and unmanageable relatives are more than annoying factors in the care of patients suffering from pneumonia.

This care in avoidance of circulatory strain should be carried out during convalescence. It is our custom to insist that the patient shall not sit up in bed until seven days after the temperature has remained at normal or below for twenty-four hours. He is then permitted to sit up in bed and the heart action carefully noted—irregularities, weakness of the pulse, even a sharp exaggeration of the sinus rhythm is a signal for return to the resting position. If no appreciable effect on the heart is noticed and the case progresses at the end of another seven days the patient is allowed to sit up out of bed. Return to normal activity should not be permitted until pulse and patient have returned to former stability and vigor.

On the question of the use of digitalis in pneumonia most clinicians of experience appear to be in remarkable unanimity. Some question still exists as to when the drug should be given, the form most desirable, dosage and the manner of administration. It is advocated by many that it should not be employed unless signs of cardiac insufficiency appear; others believe, since digitalis is a drug from

which one does not expect immediate action, even when given in its most potent form and intravenously, that its use before the specific need develops is rational. Pharmacologists appear to differ on these points, although the recent work of Canby Robinson<sup>15</sup> and others indicates a digitalis effect within a few hours with oral doses of the drug. Some argue that the best effects of digitalis are gained on normal or relatively normal muscle and that when the muscle becomes extensively degenerated the response to digitalis is less satisfactory, a belief to which we subscribe. It would seem now that most clinicians, particularly those who have had an extended experience with the treatment of pneumonia, practically agree that to get the very best digitalis effect in the disease the administration of the drug should be instituted before its need is critical.

In our opinion the best effects are obtained when the drug is given early in the disease and before the heart shows any evidence of incompetency. In so doing the adjustment to the added right heart strains is aided, and when the full strain of the disease is thrown on the heart the muscle of which has degenerated to a greater or less degree, the organ is better prepared to resist the tendency to dilatation.

It is our usual custom to give digitalis at the moment that the diagnosis is made or even when it is highly supposititious. This routine early preparation has worked out beneficially in our hands and we have seen no untoward effects from this practice. S. S. Cohen's practice of the routine use of 5 minims of a good tincture by mouth three or four times a day is, in our opinion, sound and efficient therapy. We are not in the habit of giving excessively large doses except in instances in which we believe, or know beforehand, that the heart is crippled or subnormal. In such cases we ordinarily give the drug in doses of from 15 to 20 minims every two or three hours until the rate effect appears, the pulse becomes full, the muscle sound good and the apical thrust vigorous. If then the heart appears competent the dose is reduced to 5 minims every three hours or perhaps entirely discontinued. If signs of inordinate right-heart strain appear or incompetency develops the dose is immediately increased. At such times quickly acting forms of the drug may be preferable as digipuratum, given either orally or intravenously. This particular product has proved best in our experience, though in some cases digalen, digipoten and more recently digifolin have been used with apparently excellent results.

We have a distinct preference for the routine use of the tincture of digitalis, using always the physiologically tested tinctures. Our preference, doubtless, is for the reason that we have become more accustomed to this form of the drug and therefore perhaps use it more efficiently. We have, however, no quarrel with those who prefer the infusion, the fluid extract, the powdered leaves or perhaps

one of the newer forms of the drug. The choice and results are chiefly dependent on the familiarity of the user with his particularly familiar product.

The method of early maximum administration after the outline of Eggleston we believe is by all means the preferable procedure in cases in which the heart is known to be already seriously compromised by former or present disease, but we do not employ it otherwise for the reason that our clinical experience has contented us with a dosage and administration determined by digitalis effect rather than by any fixed rule.

Of recent years there has been a swing away from the practice of using strophanthus as a substitute for digitalis. This would seem to be chiefly due to the better standardization of digitalis products. Of late the use of strophanthus intravenously has had some vogue because of the frequent need of rapid effect not possible in the absence of a thoroughly satisfactory digitalis for intravenous therapy. Recent reports from the Rockefeller Institute show that because of the inferior glass in use as containers for strophanthus there is a fluctuation of H ion content in the solution and a sharp impairment in its potency results. But when a strophanthin of high potency is used, digitalis effects may be expected rapidly. While there are cases in which sudden dramatic failure of the heart occurs in pneumonia, we believe that the use of orally administered digitalis from the first will prevent sudden giving way in most cases, and under such conditions, the recently established fact that full digitalis effect may be early realized by stomach, much of the need for strophanthin intravenously is removed. It is questionable if strophanthin intravenously can be safely employed in already digitalized patients, we believe not.

We do not wish to be understood as demanding the use of digitalis in every case and every phase of pneumonia, but we think that we voice the general opinion of most practitioners when we say that its routine use is the more advisable practice, and cases in which we do not use it are the exception. Notwithstanding the general favorable impression as to its use there are some observers who think differently. So good an authority as Stuart Hart, in a recent contribution,<sup>16</sup> throws some doubt on the wisdom of its use in pneumonia, basing his opinions on an electrocardiographic study of a limited group of cases occurring in the influenza epidemic. Hart questions also the frequency of heart failure as a cause of death in the post-influenzal pneumonia in the 1918 epidemic.

Two facts struck us in his report which may bear comment: One is that in the small amount of material which came to autopsy the hearts showed "moderate degeneration" and that a criterion of favorable digitalis effect was expected and not realized in an appreciable slowing of the pulse. Regarding pulse slowing as an indication of favorable effects from digitalis, we have Cohn's finding<sup>1</sup> that

slowing of the pulse is not a primary effect of digitalis in therapeutic doses in hearts with normal sinus rhythm.

In our experience there are no other drugs which approach digitalis and strophanthus, particularly the former, in pneumonia. We have no others which are so much to be relied upon, though for emergency medication other drugs may be properly used. Of these we have found adrenalin one of the best, particularly in those instances in which the failure is associated with marked fall in general blood-pressure or when there is a persistent decrease in pulse-pressure, which we believe to be a most important indication that this catastrophe is perhaps impending. Except for temporary use in acute circulatory emergency we have seen no beneficial results following the administration of adrenalin either subcutaneously, intravenously or by stomach. Meltzer's work shows that this drug is at times a cause of edema of the lungs and hence not too safe a one for anything like routine use as a stimulant even if it may so act.

It is no longer fashionable to give strychnine as a "cardiac stimulant" in pneumonia, but many still so use it. Edmonds and others have shown to our entire satisfaction that strychnine is not a cardiac tonic or stimulant, but that it is a depressant. There are, however, instances in which we believe that we have seen it act favorably. This is in cases which have been digitalized and in which the irritability of the heart muscle seems to be defective. Given in such instances it has on several occasions in our experience apparently increased the effect of the digitalis. We have argued on purely speculative and clinical grounds that the drug may accentuate the irritability of the heart muscle.

Camphor, usually given in ether or in oil and administered subcutaneously, we believe to be of occasional efficacy when the heart requires frequent emergency stimulation. We do not believe that its effect endures long. For results it must be given in large dosage. It is not a drug to employ as a preparatory one in pneumonia, nor can it in any way replace digitalis preparations.

We use caffein with great frequency but in precisely the same case as camphor. It is for temporary and emergency stimulation only, not for persistent use. It may be given by mouth, subcutaneously, and particularly by rectum, or by mouth in the form of black coffee, all for the same identical purpose. It probably increases a tendency toward nervous irritability and the maniacal states.

Atropin is very frequently employed by us in the circulatory management of pneumonia. We use it as an adjuvant to digitalis or of the digitalis group of drugs when they have been perhaps pushed too far and block is threatened, and particularly in those instances in which an abnormally slow action of the heart occurs, as is frequently the case in the influenzal forms of the disease. It is very useful in cardiac collapse or acute dilatation, and



in many forms of arrhythmias, just which can usually be determined clinically only by experiment. It is especially valuable, however, in cases where, due to cardiac disturbances, pulmonary or glottic edema occurs or is threatened. In our opinion it should be prescribed with great care and its administration particularly carefully observed in instances of renal disease when fluid excretion is in question or when there are evidences of a tendency toward salt retention. It may also cause anaphylactic-like reactions in many patients, and is one of the drugs toward which idiosyncrasies are most commonly manifested; even when no such active tissue antipathy toward the drug is evident it may cause a considerable degree of discomfort in a good many cases, this is oftentimes a factor well worthy of consideration in so delicately balanced a clinical disease picture as pneumonia. It is rarely a drug which is to be long continued, but rather one for temporary use in certain complications and emergencies. Next to digitalis we find it the most frequently used by us in pneumonia.

The authors have no desire whatever to claim that every drug used with benefit in the treatment of pneumonia is used because of its favorable effect on the circulatory system; it will, however, doubtless be conceded that no drug having an unfavorable effect on the circulation is very widely advised in the treatment of any phase of pneumonia. Morphin and codein are drugs which we employ not only to quiet the cough in pneumonia, which is in itself often a very important thing to do in the conservation of the circulation, but also because used when indicated they decrease restlessness and emotional irritability, promote sleep and greatly ameliorate the sufferings of the patient, even if they do not, as some assume, act directly as a stimulant on the heart muscle.

Although venesection is less frequently resorted to now than was the custom, or shall we say the fashion, a few years back, there can be no doubt of its great utility in many cases and there are few clinicians who are unaware of this fact. It is, however, not by any means a measure of general utilization and it is applicable to but a small group of cases and as a rule but for a limited period of time. We shall attempt to indicate briefly those cases and periods as they have appeared to us. In plethoric, full-blooded patients, particularly in those fat or tending to obesity, venesection often gives great physical relief from the dyspnea and the distress of the labored breathing. It is still thought by some that if venesection be vigorously employed sufficiently early it may limit the extent of or may even abort an attack of pneumonia. Few, we believe, among modern clinicians can subscribe to any such optimism, but it appears advisable and beneficial when employed early in the course of some cases, and its indications are marked dyspnea, evidence of insufficiency of the right heart in plethoric individuals, excessive cyanosis as a part of the invasion, and particularly in cases of frank hyper-

tension. In profound early toxemia, with outspoken right-heart dilatation, hypotension should not be held as an absolute contraindication. Venesection in the later stages of the disease is rarely advisable, except in those instances in which stasis from right-heart dilatation is unmistakable, and even when so indicated its result is problematical.

The amount of blood to be taken is governed by the degree of venous stasis and the reaction of the patient during the operation. As a rule it should be a substantial amount and one should lean to a generous blood-letting. When used as a means to relieve hypertension a sharp reduction in pressure or signs of cerebral anemia are the indications to stop. In low pulse-pressure states it has not been usually found an advisable procedure.

Sparteïn and many other drugs are frequently used for their cardiac effect in pneumonia. We do not discuss them here because of lack of personal experience. Each physician has learned for himself certain drugs and therapeutic measures which have proved successful in his hands; this is as it should be, but there are certain basic principles in the management of the heart in pneumonia which we believe should be always borne in mind together with a procedure best designed to meet such conditions.

A summary of these is: promotion of excretion, particularly by the bowel, of toxic material which probably contributes to the degenerative changes in the heart; the encouragement of active diuresis and the maintenance of an adequate water balance, both realized chiefly by the free use of water; the proper nourishment of the individual by means of a quickly combustible diet in which sugar and, in appropriate cases, alcoholic preparations may be advisedly used, and probably most important of all, the preparation of the heart for compensation to the initial strain and additional increments which are so strikingly a part of this disease.

We do not wish to convey the impression in this paper that we believe all cases of death in pneumonia occur as a result of cardiac disease or incompetence. We recognize fully death, as in toxic shock, with vasomotor paralysis as the most apparent symptom, cases which die from thrombosis, occasionally from acute renal defects and the like, but we do maintain that by far the most frequent immediate cause of death is from cardiac deficiency. We wish to restate our standpoint in the briefest possible way in the following conclusions:

CONCLUSIONS. 1. The most frequent immediate cause of death in all types of pneumonia is cardiac failure.

2. In by far the larger number of instances this failure is due to right-heart deficiencies.

3. This occurs because of the very limited muscle reserve capacity of the right heart, plus a myocardial degeneration, the result of toxemia.

4. The preparatory and emergency use chiefly of the digitalis group of drugs fortifies the heart against these tendencies.
5. Rest, properly timed venesection, and numerous other adjuvant measures are frequently of great therapeutic utility.

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### THE ROLE OF THE ELECTROCARDIOGRAM IN PROGNOSIS: A STUDY LIMITED TO HEARTS UNDER SINUS CONTROL AND CONTRACTING AT AN APPROXIMATELY NORMAL RATE.\*

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And in prognosis has long been sought through an interpretation of graphic records of heart-action currents. The value of a correct diagnosis as a basis for prognosis cannot be questioned. The nature of an arrhythmia can be demonstrated through a study of electrocardiographic curves. Yet the profession has been slow to avail itself of laboratory aids in the diagnosis and prognosis of irregularly beating hearts. Physicians have been even less liable to seek informa-

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tion in regard to those patients whose heart action is regular, especially if the heart-rate is not accelerated. Yet even in the latter group of hearts the electrocardiogram may furnish important information as to the state of the myocardium, information which may be essential to the forming of a correct prognosis. The object of the present paper is to attempt to assess the prognostic value of information derived from the study of electrocardiograms obtained from patients whose hearts were beating under the domination of the normal pacemaker and at a rate which was approximately normal.

Our records were collected in a general hospital in a large industrial city. The patients who were electrocardiographed were nearly all adults; the age incidence varied but the average was probably less high than would be found in many hospitals of the strictly charitable type. Patients were referred to the heart station from various departments in the hospital and by outside physicians, the services of the heart station being equally available to all. The following table indicates the source of the clinical material:

Total number of patients examined . . . . .	780	
Medical service . . . . .	480	61.5 per cent.
Gynecologic service . . . . .	67	8.5 "
Dispensaries . . . . .	49	6.2 "
Psychopathic service . . . . .	29	3.7 "
Surgical service . . . . .	11	1.4 "
Nose and throat service . . . . .	4	0.5 "
Pediatric service . . . . .	2	0.25 "
Genito-urinary service . . . . .	2	0.25 "
Obstetric service . . . . .	0	0.0 "
Unclassified as to service . . . . .	80	10.0 "
Outside physicians . . . . .	56	7.1 "
Number of cases excluded on account of ectopic origin of heart-beat or of rapid rate . . . . .	220	
Available for purpose of present study . . . . .	560	

The following abnormalities of the electrocardiogram have been considered.

1. Such distortions of the primary ventricular complex as are usually associated with conduction defects below the bifurcation of the main bundle.

2. Decreased amplitude of primary ventricular deflection as existing in the absence of other marked distortion of the electrocardiogram.

3. Prolonged *P-R* interval.

4. Invert *T*<sub>1</sub>.

5. Alternation of heart action currents or of the strength of pulse-waves as registered upon the electrocardiographic plate by means of a special device.

We fully recognize the limitations imposed upon us by the nature of the material studied: in spite of these limitations we believe that the study has not been entirely fruitless. The method carried with

it at least one definite advantage—the elimination of the element of expectant attention.

I. Distortions of the primary ventricular complex have recently been the subject of careful study.

Oppenheimer and Rothschild<sup>1</sup> have called attention to the frequent association of certain definite peculiarities of the *Q-R-S* deflections with a group of clinical conditions—arteriosclerosis, coronary artery disease, syphilis—which are liable to be accompanied by degenerative changes in the heart muscle. These authors made postmortem studies of the hearts of 14 patients from whom electrocardiograms showing distortion of *Q-R-S* deflections of a special type had been obtained during life. Disseminated sclerosis which predominated in the endocardial and subendocardial layers was found in all but one; the prognosis in the presence of the described distortion of the electrocardiogram was believed to be grave.

The electrocardiogram which these authors believed associated characteristically with this type of myocardial involvement (which results in “disturbed intraventricular conduction”) is described as follows:

1. Abnormal prolongation of the time interval of the *Q-R-S* group beyond the normal limit of 0.1 second.
2. Notching of the *R* wave.
3. Occasional low amplitude of the waves in all leads.
4. Absence of the typical diaphasic curves, with large  $T_1$  waves, as found in experimental branch bundle block.<sup>2</sup>

Carter<sup>2</sup> concludes that “the presence of a predominant sclerosis of the terminal arborizations of the Purkinje system gives rise to electrocardiographic curves of low amplitude associated with a bizarre ventricular complex of a definite type. Curves of large amplitude, essentially diphasic, may justly be regarded from experimental evidence available, as indicative of a definite totally obstructive temporary or permanent lesion of one of the branches of the atrioventricular bundle. The presence of curves of low amplitude, so characteristic of a diffuse sclerosis, did not, however, preclude the existence of definitely localized focal lesions involving the main stem and its branches.”

Robinson,<sup>3</sup> while accepting the conclusions of Oppenheimer and Rothschild<sup>1</sup> as applicable to a group of cases, has shown that a like distortion of the electrocardiogram may occur occasionally as an expression of what he believes to be temporary functional fatigue.

<sup>1</sup> Electrocardiographic Changes Associated with Myocardial Involvement, Jour. Am. Med. Assn., August 11, 1917, lxi, 429.

<sup>2</sup> Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med., September, 1918, xxii, 331.

<sup>3</sup> Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med., October, 1919, xxiv, 422.

Willius<sup>4</sup> states that arborization block is now generally accepted to indicate disease of the subendocardial myocardium and evidences serious functional cardiac disturbance.

Robinson's hypothesis added to the conclusions of Carter seems to be a fair summary of the present knowledge of block below the bundle of His.

A study of our records has convinced us that it is occasionally impossible to classify distortion of  $Q-R-S$  by the criteria of Oppenheimer and Rothschild.<sup>1</sup> Borderline records occur in which it is only possible to assign the block to a point below the main stem of the bundle. Furthermore, one cannot always prove that the block arises as the result of histologic lesion. Thus we have been unable to exclude the fatigue element in several of our cases, since some of our patients have presented themselves for examination but once. However, in no case have we noted a return to normal after the distortion of  $Q-R-S$ .

Our material consists of records of 19 patients, or a total of 3.4 per cent. of the patients with sinus rhythm: 60 per cent. of the patients were males. The average age incidence was fifty-seven; the youngest patient was thirty-five years old. Most of the patients presented the clinical picture of cardiorenal vascular disease. Syphilis is conspicuous by its absence. In only one case was a positive blood Wassermann obtained, this patient having an aortic insufficiency. In 10 cases the Wassermann was negative, as were history and evidence gained by physical examination. No Wassermans were taken on any of the 8 remaining patients. In none of these was a clinical diagnosis of syphilis made, and in at least 2 of the 8 it is probable that the disease can be almost definitely excluded.

Measurement of serial plates showed that the width of the  $Q-R-S$  interval varied from time to time, as between 0.10 and 0.14 in one patient and 0.16 and 0.20 in another. However, widening, having once been established in a given case, the  $Q-R-S$  interval subsequently was never found to decrease below 0.1. The persistence of a given form of distortion, as established by an individual, has been striking at times. The following case is reported as illustrative:

W. H., male, aged seventy-three years. Admitted November 20, 1915, complaining of dizziness, weakness, dyspnea and swelling of the feet. The diagnosis was cardiorenal vascular disease. The patient remained under observation for four years. He died a cardiac death, December 11, 1919. No postmortem could be obtained. Electrocardiographic curves on admission showed sub-bifurcation block. The accompanying figures show that a change in contour of curves occurred during the first sixteen months, with but little change during the subsequent twenty-one months.

In regard to nearly all of the patients in this group there was

<sup>4</sup> Arborization Block, Arch. Int. Med., April, 1919, xxiii, 431.

sufficient clinical evidence to enable one to make a diagnosis of an underlying cardiosclerosis. That there are exceptions to this rule is shown by the following case:

H. J. M., male, aged fifty-seven years, clerk. Referred by an oculist for relief from headache: no sclerosis of retinal vessels; palpable vessels unusually soft for age; no symptoms referable to heart, which was apparently normal. Blood-pressure, 110-76. The arteriogram showed slight irregularity of the height of the pulse-waves but was otherwise normal; phthalein excretion (intravenous), 78 per cent. in one and a half hours; peridental infection; chronic sinusitis; pulmonary tuberculosis. Of two electrocardiograms taken at an interval of three weeks, both showed subbifurcation block.

The patient was markedly toxic during the period of observation. Unfortunately an opportunity has not arisen to examine him at a time when his heart muscle was carrying a lighter load. It is not impossible that this patient might subsequently have a return to normal contour of electrocardiogram.

Of our 19 patients, 9, or 40.7 per cent., are dead. Of these 6 lived less than four months after block was demonstrated. One died after a period of four years. Two are alive in whom the distortion was noted forty-five and forty-eight months ago.

We believe that the above statistics are confirmatory of the growing belief that a definite deformity of the *Q-R-S* deflections is often associated with extensive myocardial degeneration and that this finding should be sought for as part of routine in the case of patients showing evidence of cardiorenal vascular disease. Prognosis regarding this group of patients, can usually be made by an experienced clinician without laboratory help. However, the routine examination as carried on in a heart station may be of great value by indicating that certain patients should be referred to an internist before subjecting them to operation or discharging them from the hospital. In occasional cases electrocardiographic evidence of myocardial degeneration may occur in the absence of obvious signs of the disorder. It should be remembered that subbifurcation block may occur as a result of a temporary condition, such as overfatigue or toxemia. Consequently, in doubtful cases repeated observations may be essential.

II. Decreased amplitude of primary ventricular deflections may exist in the absence of other distortion of the form of electrocardiogram. There may be considerable variation in the height of the primary complexes in electrocardiograms of normal individuals. Thus, Lewis<sup>5</sup> found that if a series of curves be taken from a number of active students the minimum in the three leads was 1.5, 4 and 2 respectively, while the maximum was 10, 16.5 and 14 scale divisions. The average of 59 students examined was: Lead I, 5.16; Lead II,

<sup>5</sup> Clinical Electrocardiography, London, Shaw, 1913, p. 22-23.

10.32; Lead III, 6.61. Nevertheless, Lewis believes that considerable divergence from what is regarded as normal probably indicates that the heart is abnormal. White<sup>6</sup> states that "not infrequently one finds electrocardiographic evidence of a very weak myocardium in cases with a regular pulse. This is shown by one of two findings, a very low flat *T* wave (when one can rule out digitalis) and a small excursion of all waves in all leads." He concludes that very small deflections in all leads usually indicate a very weak myocardium. Frazer<sup>7</sup> noted, as a result of experimentally induced dilatation of rabbits' hearts, that a diminution of the size of all the waves of *Q-R-S* group was observed in degenerative conditions of the heart muscle. Oppenheimer and Rothschild<sup>1</sup> employed low amplitude of the primary ventricular complex as one of the criteria for recognizing the electrocardiogram which was associated with myocardial involvement with a bad prognosis.

In selecting a standard for sorting of our electrocardiograms, we have accepted ten scale divisions as the average normal. This has been done in full realization that each patient must establish his own normal and that any standard is therefore an artificial one. At most such deductions can be only inferential. Further sources of error may be due to instrumental defects and faulty technic. There was an occasional unexplained variant as illustrated in Fig. 4. In numerous instances the possibility of instrumental defect appears to have been excluded definitely by the fact that control electrocardiograms gave normal deflections. In a small group of patients there existed so striking a parallelism between lower amplitude and increasing myocardial insufficiency that the association could hardly have been accidental in all of them.

Of our patients, 46, or 5.8 per cent., showed constant or occasional low voltage in all leads; 56 per cent. were females. The age incidence differed widely. The mortality was relatively high: 17, or 36 per cent., are dead. Of the total deaths, 76 per cent. occurred in patients in the fifth decade.

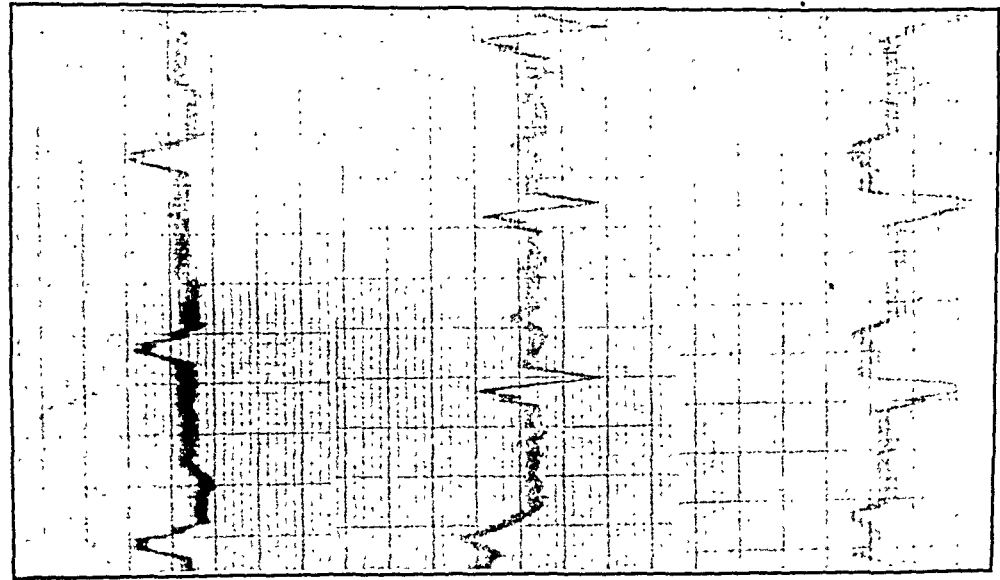
The following case illustrates a changing amplitude exactly parallel to the clinical condition at the time the records were taken. It is believed that the electrocardiograms may be depended upon as each record was checked by control patients.

E. F. D., male, aged twenty-four years, admitted February 3, 1920. Clinical diagnosis; pericardial effusion; at first serous; later purulent. Effusion drained, April 14, 1920. The primary deflection of first electrocardiogram was eight scale divisions. This record was taken at a time when the patient was able to walk about, with apparent comfort. Subsequent curves taken at periods during

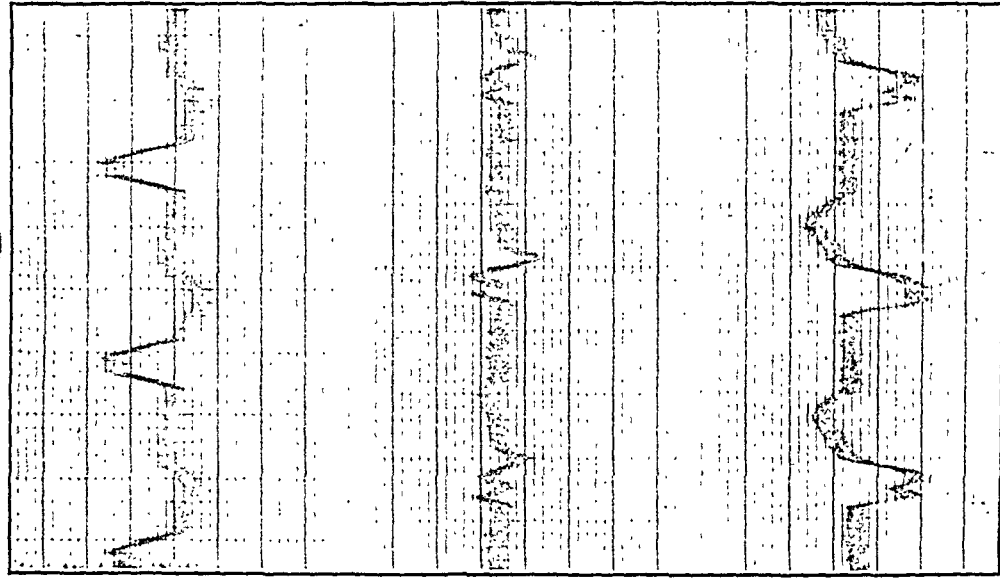
<sup>6</sup> Diagnostic Value of Electrocardiography of Hearts Beating Regularly, *Med. Clinics of North America*, January, 1920, iii, 1035.

<sup>7</sup> Changes in the Electrocardiograms Accompanying Experimental Changes in Rabbits' Hearts, *Jour. Exper. Med.*, September, 1915, xxii, 292.

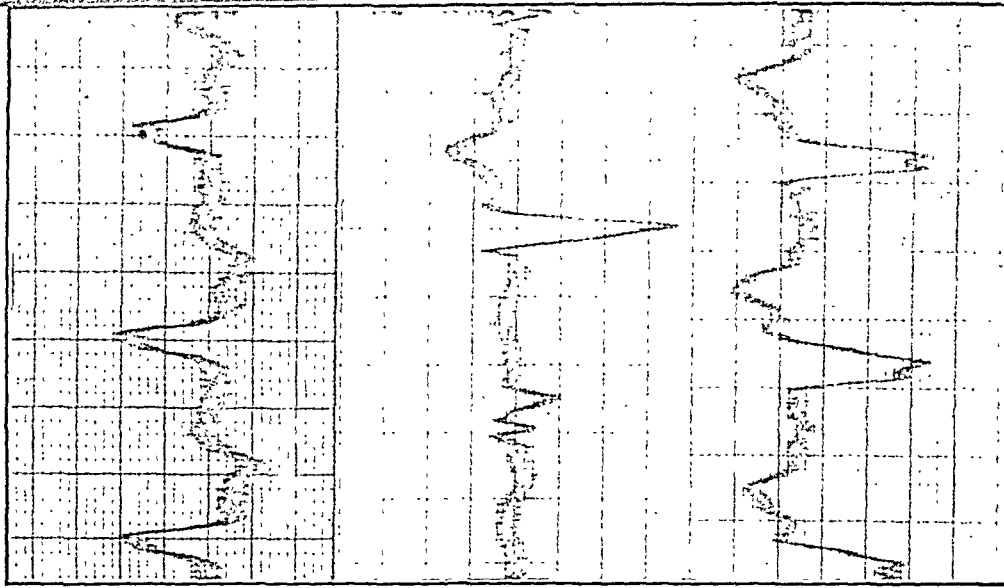




A. November 27, 1915.



B. April 17, 1917.



C. January 4, 1919.

FIG. 1.—Sub-bifurcation block: *B* and *C* are similar, yet a period of twenty-one months intervened. *A* illustrates the difficulty in localizing definitely the seat of the block. It is possible either that the block began in the finer ramifications of the bundle, later extending to the main branch, or that the block occurred in the larger branches from the onset.

which the patient's clinical condition became progressively worse, showed a progressive diminution in amplitude to two scale divisions. A final record taken during a period of improvement after operation showed a return to wider deflections (four scale divisions).

That conclusions based on progressive decrease of amplitude might result in error is exemplified by the following:

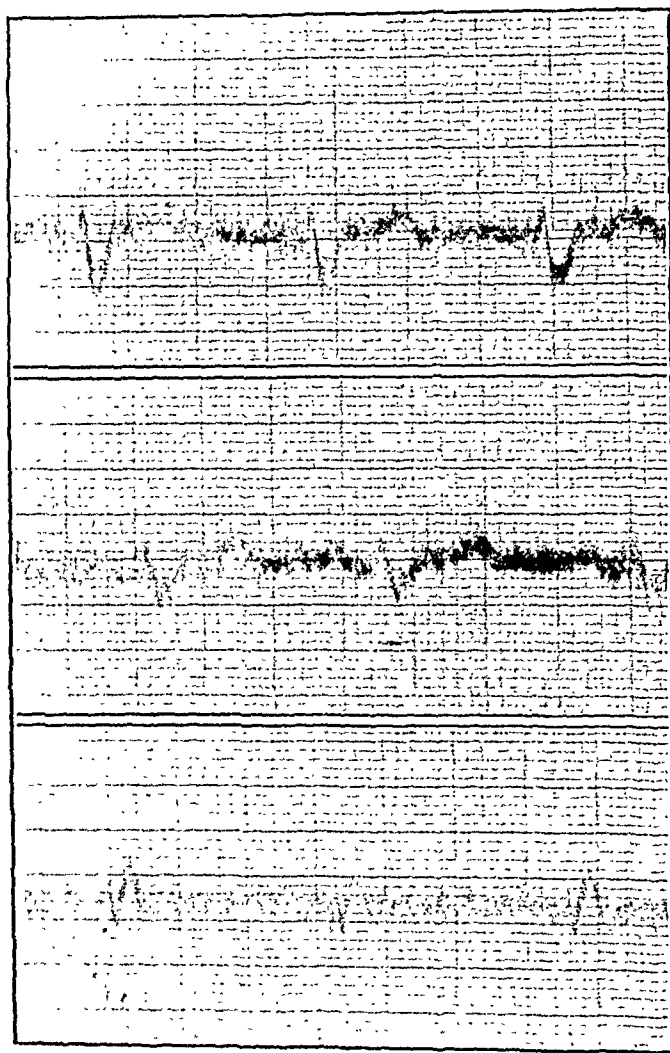
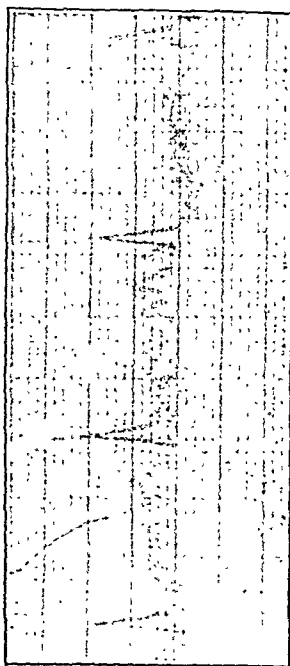
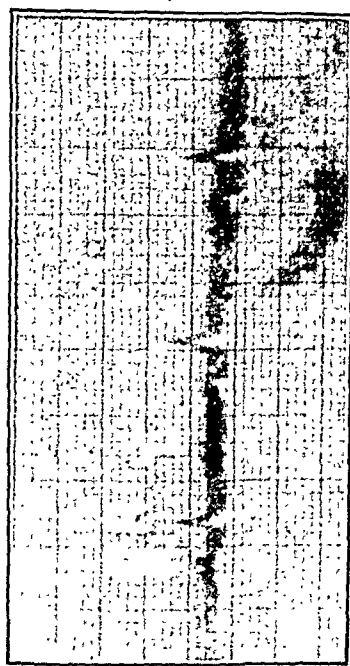


FIG. 2.—Sub-bifurcation block: Occurring in a patient without symptoms, suggesting cardiac disease. H. J. M., aged fifty-seven years. Referred by an oculist for headaches.

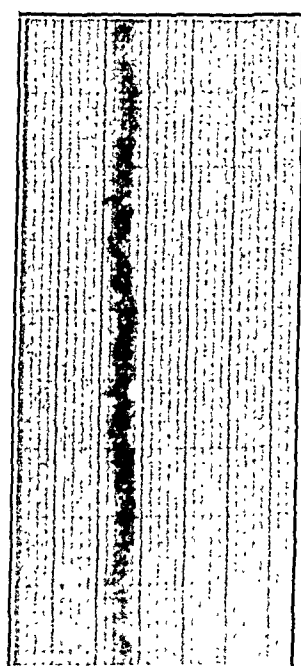
R. G., female, aged seventy-eight years. Admitted May 11, 1916. Clinical diagnosis: acute endocarditis superimposed upon chronic mitral and aortic valvular disease; chronic myocarditis; pulsus alternans. Clinical condition of patient became progressively worse while in the hospital. Electrocardiogram on admission showed normal height of deflections, ten scale divisions, Lead I. Patient



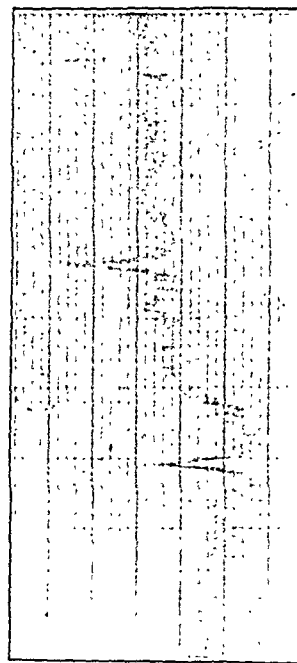
A. February 3, 1920. E. F. D., aged twenty-four years. Sero fibrinous pericarditis of tubercular origin; effusion, later becoming purulent. Patient able to walk without dyspnea.



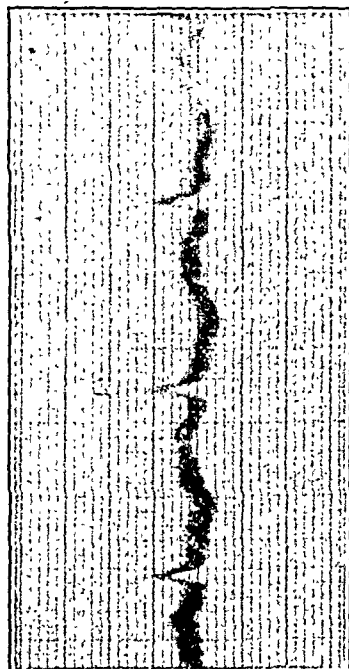
B. March 29, 1920. Effusion more marked. Decompensation severe.



C. April 16, 1920. Forty hours after drainage of pus from pericardial cavity. Extreme weakness. Circulation poorly maintained.



D. April 16, 1920. Control.

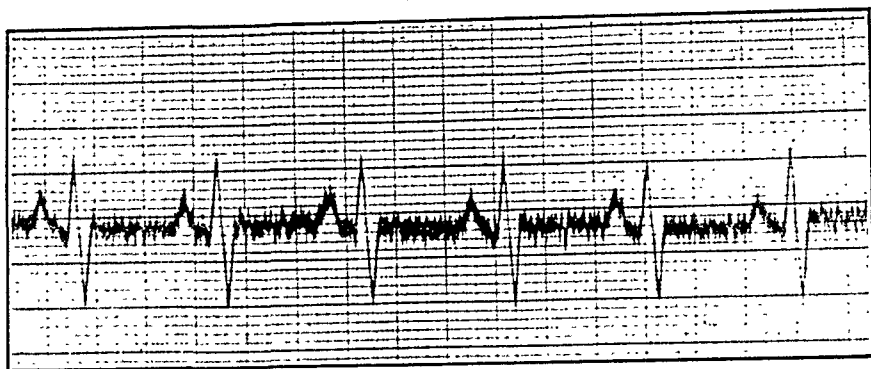


E. April 29, 1920. Increased amplitude thirteen days after operation. Subjective and objective improvement.

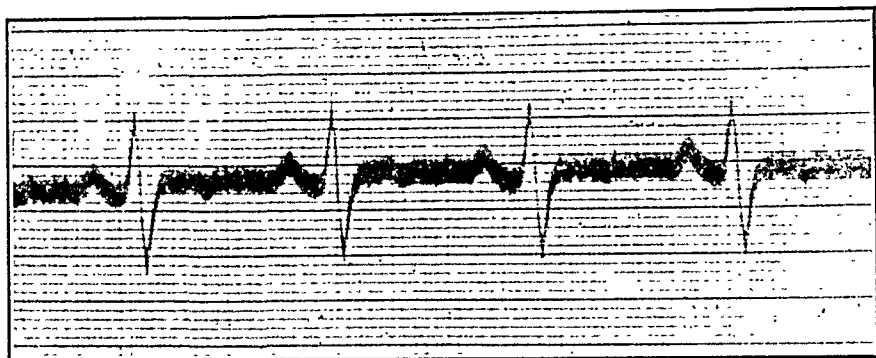


F. April 29, 1920. Control. Height varying with clinical condition.

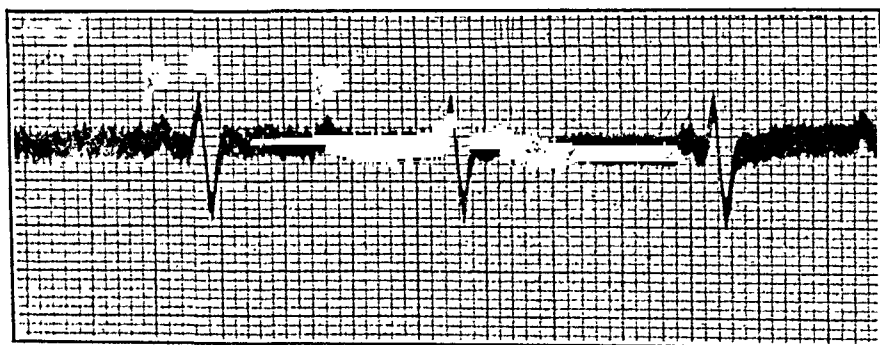
Fig. 3.—Decreased amplitude.



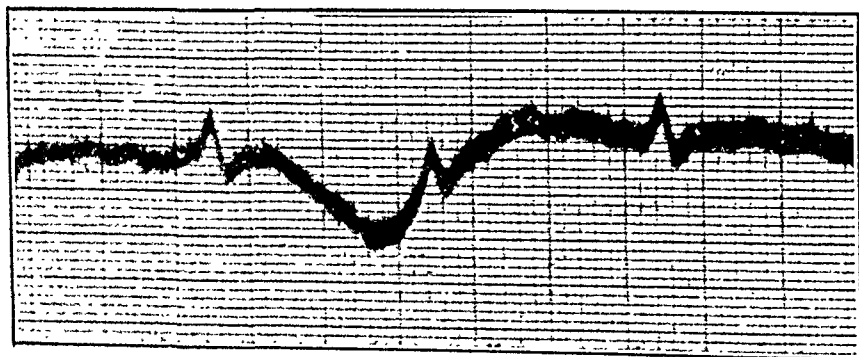
A. June 13, 1916.



B. February 3, 1917.



C. March 6, 1917.



D. April 6, 1917.  
FIG. 4.

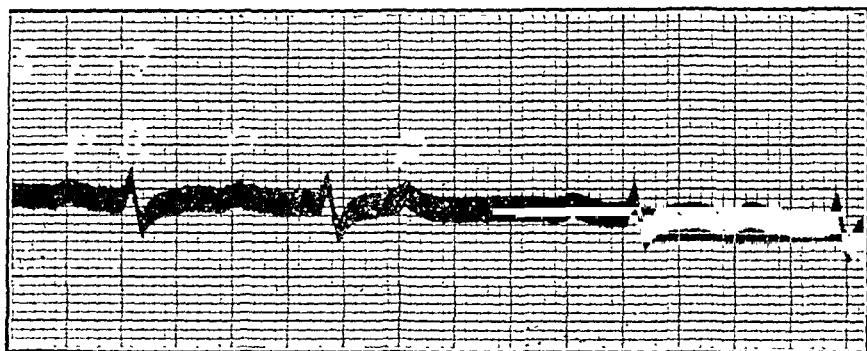
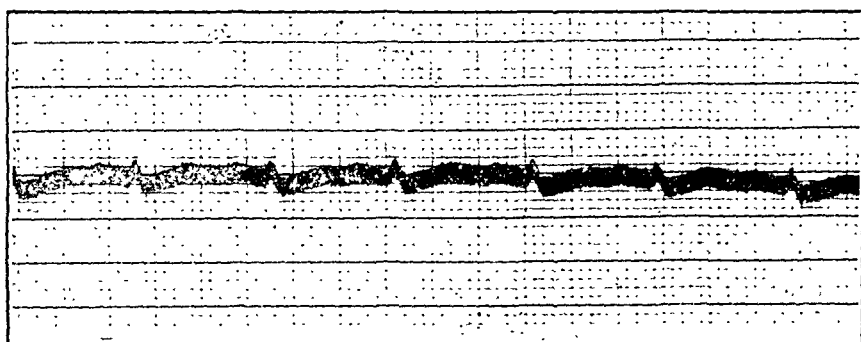
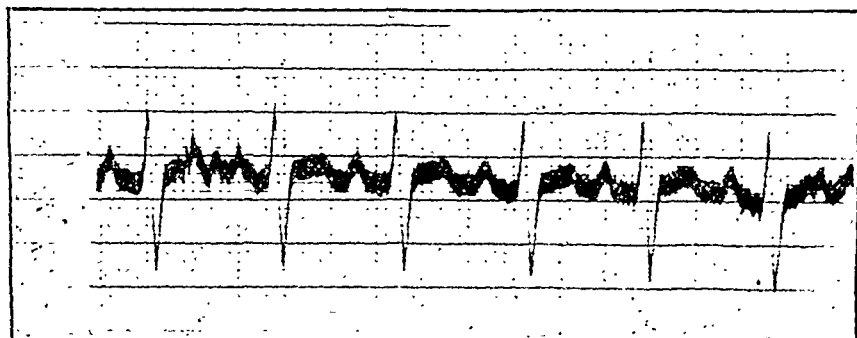
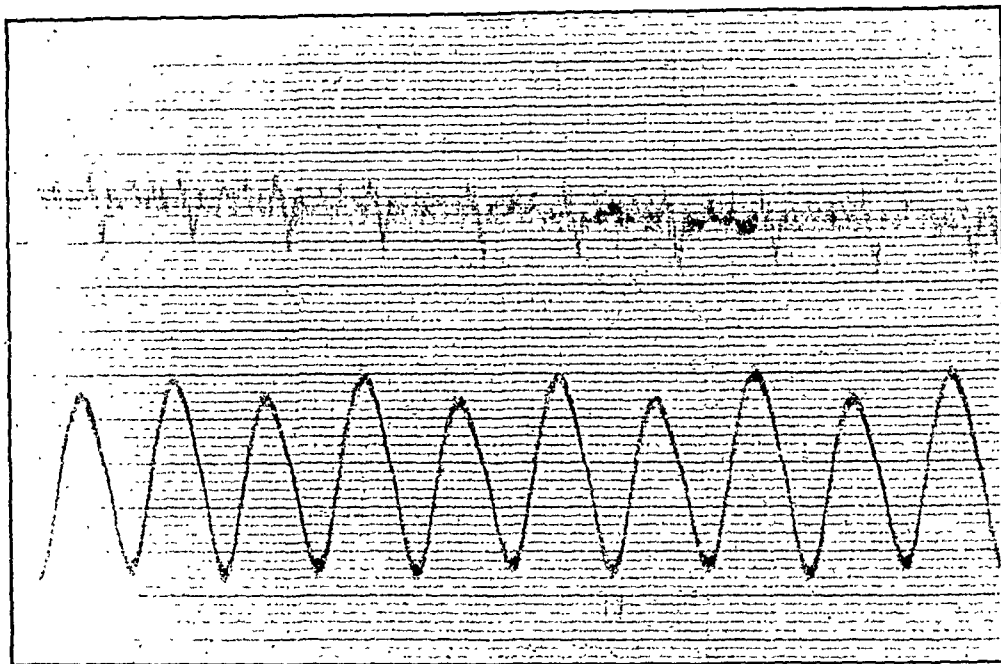
*E. May 1, 1917.**F. May 15, 1917.**G. May 18, 1917.*

FIG. 4a.—Decreased amplitude. Height varying with clinical condition during period of eleven months; sudden return to normal amplitude nineteen days before patient's death and at period when decompensation was profound. R. G., aged seventy-eight years. Acute endocarditis, superimposed upon chronic mitral and aortic valvular disease. Chronic myocarditis; pulsus alternans.

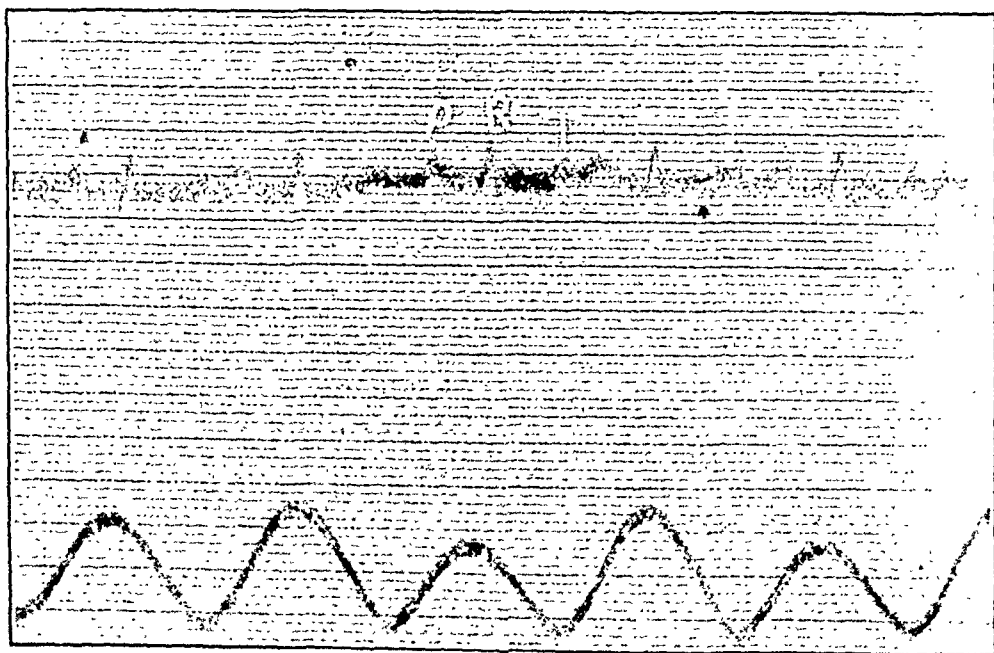
discharged November 2, 1916, no further electrocardiogram being taken. Readmitted January 4, 1917. Patient died June 6, 1917. Patient's clinical condition became progressively worse after second admission. The amplitude of the primary deflections became gradually smaller (from seven to one scale divisions). However,

there was one striking exception; a final electrocardiogram nineteen days before death showed that the deflections had returned to ten scale divisions.



A. Pulsus alternans.

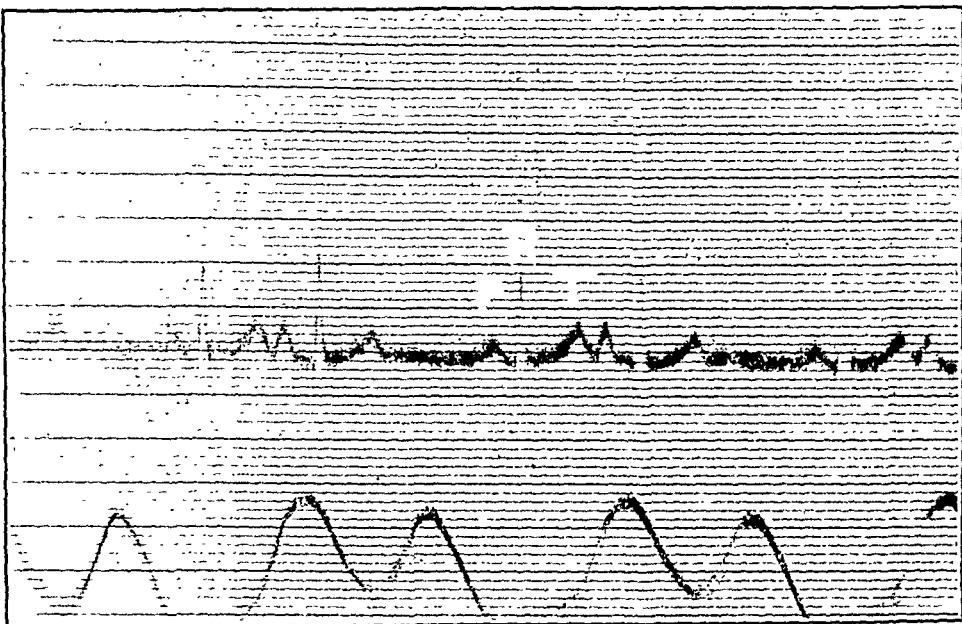
FIG. 5.



B. Pulsus alternans.

FIG. 5a.

III. Prolongation of the  $P$ - $R$  interval over the normal of 0.2 second may be due to various causes such as acute infections, drug action and degenerative processes affecting heart muscle. There is considerable difference of opinion among observers as to the normal  $P$ - $R$  interval. Lewis<sup>8</sup> states that "prolongation over 0.20 second is never found in healthy hearts." Hecht<sup>9</sup> regards 0.14 as normal; F. N. Wilson<sup>10</sup> accepts 0.17. Within certain limits each patient sets his own standard. Cohn, Jamieson and Frazer<sup>11</sup> have shown



C. Coupling due to premature beats; patient referred to heart station as case of supposed alternation.

FIG. 6.—Type of tracing obtained by apparatus illustrated in Fig. 7.

that digitalis can prolong the  $P$ - $R$  interval. Hence unless digitalis influence can be excluded, no conclusions as to prognosis can be based upon prolongation of the  $P$ - $R$  interval. Such deductions could not be made in patients of our series since regarding most of them no reliable history as to previous medication was available. On the other hand it is exactly in the type of patient in which a prolongation of  $P$ - $R$  interval might be expected that digitalis is most liable to be administered.

<sup>8</sup> Vide supra, p. 37.

<sup>9</sup> Der Mechanismus der Herzaktion im Kindersalter, seine Physiologie und Pathologie, *Ergeb. d. inn. Med. u. Kinderh.*, Berlin, 1913, ii, 324; quoted by Rupe: *Mod. Med.*, March, 1920, ii, 215.

<sup>10</sup> Recent Progress in Pediatrics, *Résumé on the Circulation*, *Am. Jour. Dis. Children*, 1915, x, 376; quoted by Rupe: *Loc. cit.*, p. 215.

<sup>11</sup> The Influence of Digitalis on the T-wave of the Human Electrocardiogram, *Jour. Exper. Med.*, June, 1915, xxi, 593.

IV. Since such inversion is always or nearly always pathologic, according to Lewis<sup>12</sup> inversion of  $T_1$  "is often associated with signs or symptoms of ill omen." This author published figures<sup>13</sup> in which an invert  $T_1$ , which followed temporary deformity of primary ventricular complex, became upright when that deformity disappeared. The first curve was taken during a febrile attack, the second, one day later, after the subsidence of fever. Willius<sup>4</sup> states that a close connection exists between inversion of  $T_1$  and disease of myocardium. Cohn<sup>11</sup> and his associates have shown that digitalis can modify  $T$  in that a  $T$  which was upright in the initial curve may be lowered first and finally inverted. Inversion of  $T_1$  has been noted by White<sup>6</sup> in connection with hypothyroidism the  $T$  "tending to become more positive" in the presence of clinical improvement during thyroid feeding. Morrison<sup>14</sup> has noted that changes in the electrocardiogram following bleeding, hot-packs, ingestion of water and fasting may in certain persons affect the form of the electrocardiogram. Harris<sup>15</sup> while admitting that digitalis may affect  $T_1$ , draws definite conclusions on inversion of  $T_1$  as observed in 16 of 40 patients electrocardiographed in an out-patient clinic. The cases electrocardiographed were selected on account of dyspnea on exertion, fainting fits and edema. Apparently no history of previous medication was sought, since no mention of absence of digitalization is made in this author's text or accompanying table; yet Harris has the temerity to conclude that "an invert  $T$  in the Lead I is reliable evidence of a damaged heart muscle."

Fifty-three cases in our series show inversion of  $T_1$ . In 26 of these  $T_1$  was inverted alone. In only 1 case was it possible definitely to rule out digitalis. Hence we are unable to draw any deductions as to the significance of invert  $T_1$  as personally observed.

V. From the standpoint of prognosis, alternation of the pulse, as occurring in hearts beating at an approximately normal rate, is a finding of extreme gravity. Unfortunately the electrocardiograph is capable of recording only the alternation of heart-action currents. The fact that curves showing such a disturbance of mechanism are rare is confirmed by our series in which the finding was present regarding but 0.55 per cent. of all patients examined. It is unfortunate that the electrocardiograph is incapable of demonstrating the disturbance of mechanism underlying the alternating pulse, since the latter finding, if sought for as routine, is found to be of frequent occurrence. Obviously, the value of the string galvanometer would be enhanced if it were possible to record simultaneously

<sup>12</sup> Clinical Electrocardiography, London, Shaw, 1913, p. 28.

<sup>13</sup> Idem, p. 29.

<sup>14</sup> Changes in the Electrocardiogram due Possibly to Alterations in Blood Volume, Proc. Soc. Exper. Biol., and Med., 1916-1917, xix, 64.

<sup>15</sup> Significance of an Inverted "T" in the First Lead of the Cardiogram, Lancet, February, 1919, i, 168.



electrocardiograms and pulse-waves. Our discussion of alternation will be limited to the description of an apparatus which we have devised to fulfil this indication.

The device which we are using combines the simplicity of the cuff method of Herrick<sup>16</sup> with the accuracy of the electrocardiogram. It therefore obviates the various sources of error of the former while preserving much of its simplicity of application. Used by us first only when a sphygmograph was not available, it is now used as routine on all arteriosclerotic patients and on those exhibiting premature contractions. The apparatus which is both time-saving and inexpensive may be visualized by reference to the accompanying illustration (Fig. 7).

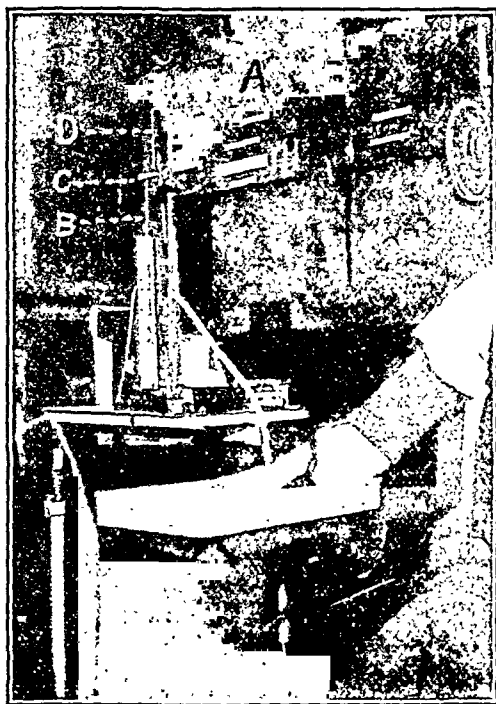


FIG. 7.—Recording apparatus for reading pulse waves in connection with simultaneous electrocardiogram; used for detection of pulsus alternans. A, camera; B, straw attached to cork float which rides on mercury; C, transverse arm of lever, which rests on straw; D, upright arm of right-angled lever, which oscillates in front of camera lens.

The oscillations of the mercury column of a sphygmomanometer are transferred to a right-angled lever, the upright arm of which moves in front of the slit of the camera of an electrocardiograph. The cuff of the sphygmomanometer is applied in the usual manner and the tracing is taken at a pressure slightly below that ordinarily accepted as the systolic pressure.

<sup>16</sup> Pulsus Alternans Detected by the Sphygmomanometer, Jour. Am. Med. Assn., February, 1915, lxiv, 739.

We claim no originality in the production of a combined electrocardiogram and pulse-tracing. Methods of producing such combined records abound. It is even quite possible that other investigators have employed the principle upon which our appliance is based. As we have seen no reference in the literature to such an application, however, we feel justified in describing it here. The accompanying figures are illustrative of the results obtained.

**Conclusions.** 1. Electrocardiographic curves are capable of furnishing important information as to the efficiency of the heart muscle.

2. As cardiac failure is due to myocardial insufficiency the electrocardiograph can furnish information valuable from the standpoint of prognosis.

3. Conduction defects below the bifurcation of the bundle of His may be associated with a characteristic electrocardiogram. It is often difficult to determine whether such defect is in the branch bundle or in the terminal arborization. The defect may be functional or it may be due to histologic change. In the latter case the prognosis is grave.

4. Decreased amplitude of the primary ventricular deflections is at times found to have a striking relationship to clinical evidence of a failing heart. Exceptions to this relationship occur, and, as there are several possible sources of error in obtaining reliable curves, observations should be carefully controlled and definite conclusions withheld until the subject is further elucidated.

5. Prolongation of  $P-R$  interval and inversion of  $T_1$  have been associated by various observers with degenerative processes in heart muscle. A prolongation of  $P-R$  and an inversion of  $T_1$  can also be brought about by digitalis action, and it is precisely in the class of cases in which information as to the  $P-R$  interval and inversion of  $T_1$  could be of value that digitalis is liable to have been administered. Conclusions as to the condition of heart muscle as based on the presence of one or the other of these deformities must be confined to patients from whom digitalis effect can be excluded. Analysis of our series has shown that digitalis effect can seldom be excluded in such patients as are routinely referred to a heart station. Hence, prolongation of  $P-R$  and inversion of  $T_1$  are liable to be of little prognostic significance in such patients.

6. A discussion of pulsus alternans does not come properly within the scope of this paper, since the underlying disturbance of mechanism can seldom be demonstrated by the string galvanometer. This fact is unfortunate, since the recognition of an alternating pulse carries with it so grave a prognosis that the search for this finding should be routine in certain classes of patients. A simple device is described whereby galvanometric curves and pulse waves can be simultaneously recorded. This can be done with but little expenditure of time, and the method has therefore become routine in our laboratory.

7. The practical value of laboratory evidence as to the presence of disease of the heart muscle is inversely proportionate to the skill of the attending physician in interpreting clinical evidence as to the imminence or presence of heart failure. Such skill is possessed chiefly by the internist. Yet internists furnished 61.5 per cent. of all cases examined. The statistics of other heart stations would probably be similar. It becomes, therefore, the duty of the internist to instruct members of other branches of the profession regarding the necessity of more frequent use of instruments of precision in the diagnosis and prognosis of disease of heart muscle.

NOTE.—The authors acknowledge their indebtedness to Dr. A. P. D'zmura for assistance in the preparation of this paper.

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## OBSERVATIONS ON NEGATIVITY OF THE FINAL VENTRICULAR T WAVE OF THE ELECTROCARDIOGRAM.\*

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A REVIEW of the literature on electrocardiography, both experimental and clinical, at once reveals a variance in views as to the interpretation of the normal electrocardiogram. The two views that have gained broadest recognition are: (1) All waves are manifestations of excitation and contraction of heart muscle, and (2) the waves result from electric changes accompanying conduction of the impulse and contraction of the muscle.

Einthoven assumed that the right ventricle represents the cardiac base and the left ventricle the apex, and that the dominance of negativity in the right ventricle causes an upward deflection while dominance in the left causes a downward deflection of the galvanometer. Thus the *R* wave is ascribed to contraction of the right heart, the *S* wave to contraction of the left heart and the horizontal *S-T* interval to neutralization of basal and apical negativity. The *T* wave represents contraction of the right ventricular base outlasting that of the left.

Eppinger and Rothberger object to Einthoven's assumption in ascribing the rôle of cardiac base to the relatively weak right ventricle and regarding the left ventricle with its massive muscle bulk as the apex.

The views of Kraus and Nicolai are based on the structural arrangement of the ventricular musculature into systems. Follow-

\* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the Degree of Master of Science in Medicine, May, 1920.

ing auricular contraction the impulse passes through the auriculo-ventricular bundle and its contiguous structures. The long *P-R* interval is explained by slow conduction and the absence of appreciable action currents at this time due to the small muscle mass. The *R* wave is ascribed to primary activity of the basal portions of the papillary muscles. As the excitation wave spreads toward the apex the termination of the *R* wave occurs. The *S-T* interval is explained by the absence of potential between base and apex. The *T* wave results from late return of negativity to the base.

The views of Einthoven, Kraus and Nicolai agree in general in emphasizing the antagonistic action of electric potential between base and apex.

In distinct opposition to the views already expressed, Hoffmann concluded that the electrocardiogram results from two actions, impulse conduction and muscle contraction. The *Q R S* complex results from passage of the impulse through the ventricular conduction system and the *S-T* interval and the *T* wave from electric potential caused by the contracting ventricle. Hoffmann produced standstill of the frog heart by the application of muscarin, obtained simultaneous electrocardiographic and ventricular suspension curves and found that the electrocardiogram of the non-beating heart differs from the normal only in the absence of the *T* wave. When the muscarin effect was abolished by atropin and the beats returned the *T* wave reappeared.

Eyster and Meek, as a result of their experimental work on the relation of the line of isopotential to the formation of the electrocardiogram and their critical review of the literature, in general agree with Hoffmann's theory. They believe the *R* wave to be concerned with conduction, but they do not ascribe definite structures as conducting mediums. The *T* wave is the expression of preponderance of contraction on one side of the line of equipotential. Eyster and Meek further show the differences between physiologic curves of conduction and contraction. When a nerve is stimulated where conduction alone occurs a single monophasic or diphasic electric response occurs. In skeletal muscle this rapid electric change is followed by a slower and more prolonged electric variation. This conforms with the general contour of the electrocardiographic deflections; the *R* wave is abrupt and steep, the *T* wave blunt and prolonged.

#### CARDIAC EVENTS AND THE ELECTROCARDIOGRAM.

The relationship of the waves of the electrocardiogram to definitely known cardiac events strongly supports the "conduction contraction" theory. By a consideration of accepted relationships of the normal heart sounds a working basis for comparison is established.

Einthoven, Flohil and Battaerd have shown that the first sound begins at the initiation of ventricular systole and lasts from 0.07 to 0.10 second, is followed by a pause varying from 0.15 to 0.25 second and then succeeded by the second sound. These observations have been confirmed by other investigators.<sup>1 10 35</sup> The second sound follows closely on the closure of the semilunar valves,<sup>37</sup> begins simultaneously with the rise of intraventricular pressure<sup>14</sup> and gains its maximum amplitude during this period.<sup>33</sup> That the second sound is an early diastolic event has been shown clearly.<sup>26 36</sup>

Kahn has demonstrated that the first sound falls in the pause between the *R* and the *T* waves and begins at the moment the *R* wave disappears and a short time before the rise of the *T* wave. The second sound begins 0.05 second after the end of the *T* wave. This relationship reveals the fact that the *R* wave is completed before ventricular contraction begins and indicates conduction rather than contraction. The *T* wave definitely occupies the period associated with actual ventricular contraction.

In clinical studies of the abnormalities of the *Q R S* group they are largely ascribed to disease of the ventricular conduction system.<sup>3 24 34 38 31</sup> It must be recognized, however, that the graphic representation of contraction in the electrocardiogram is the expression of changes in electric potential and not the translation of actual contraction. The iso-electric portion of the intervals *S-T* and a portion of *T-P* are not latent in the sense of a refractory phase.

### CONSIDERATION OF ELECTROPOTENTIAL.

Waller and Reid demonstrated a line of equipotential passing through the heart from base to apex in relation to any two derivations from the extremities. A preponderance of negativity above this line, representing the cardiac base, caused deflection of the galvanometer connected to both upper extremities in a manner to indicate relative negativity of the electrode connected with the right arm. The arm becomes relatively negative in derivations from an arm and a leg. Dominance of negativity below the equipotential line deflects the galvanometer in the opposite direction.

### HYPOTHESIS OF *T*-WAVE NEGATIVITY.

The three derivations of the electrocardiogram possess symbols of definite electropotential in relation to their electrodes. In the normal electrocardiogram derivation 1 bears symbols as follows: right arm —, left arm +; derivation 2, right arm —, left leg +; and derivation 3, left arm —, left leg + (Fig. 1). This arrangement implies positive or upright deflections in all derivations of the electrocardiogram. If it is assumed that the "conduction-con-

traction" theory is correct the *T* wave is the expression of preponderance of contraction on one side of the line of equipotential. *T*-wave negativity (inverted) therefore results from changes in contraction preponderance. The negativity of this wave in certain isolated or combined derivations of the electrocardiogram is indicative of definite potential changes affecting contraction preponderance in various regions of the cardiac musculature.

In the normal heart, therefore, according to standard derivations, the *T* wave in all derivations is positive (upright), the upper right zone of potential is strongly electronegative to the apical zone while the left upper zone is iso-electric. This potential arrangement is illustrated in Fig. 1.

For reasons of simplification I have represented the three derivations by the sides of an equilateral triangle. To prevent misunderstanding it should be stated that the schematic figure employed, divided into zones of electropotential, is not based on mathematic consideration. The right upper zone in general corresponds to the sinus region of the heart and in the normal potential arrangement is electronegative.

Confirmation of this is found in the researches of Keith and Flack, Wybauw, Lewis, Oppenheimer and Oppenheimer, Brandenburg and Hoffmann, and Ganter and Zahn, who have shown that the cardiac impulse takes its origin in a collection of specialized tissue, a remnant of the primordial sinus. This structure lies in the sulcus terminalis at the juncture of the superior vena cava and the right auricular appendage, and is the seat of primary cardiac negativity.

Changes in the normal potential distribution produce *T* wave negativity in isolated or combined derivations of the electrocardiogram. Reversal of potential in one derivation alters cardiac potential so that *T*-wave negativity in that derivation occurs.

### *T*-WAVE NEGATIVITY.

Many opinions have been expressed as to the significance of negativity or inversion of the *T* wave in isolated or combined derivations of the electrocardiogram.

The effect of digitalis on the heart as manifested by negativity of the *T* wave is well known;<sup>4</sup> it has been ascribed to muscular ventricular redistribution or possibly to alteration in muscular contractility. These changes are not permanent.

Numerous statements may be found in which myocardial damage is ascribed to *T*-wave negativity in certain derivations,<sup>3 18 19 23</sup> and again these occurrences have been noted in apparently normal hearts<sup>15 20 31</sup> affecting largely derivation 3.

Smith during his experimental work on coronary ligations observed interesting changes in the *T* wave. The most constant

Positive T wave in all Derivations (normal)

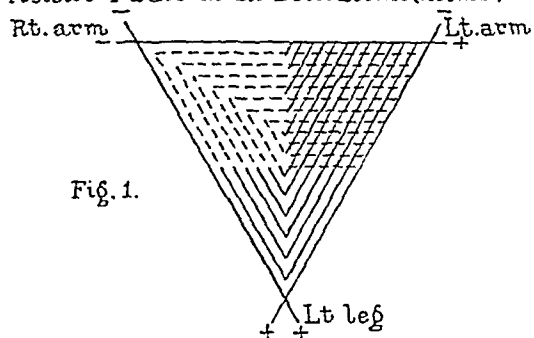


Fig. 1.

Negative T wave in Derivation I.

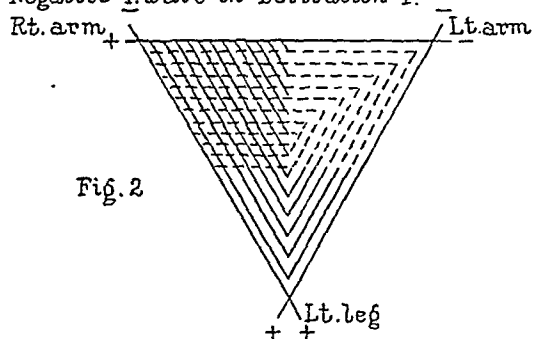


Fig. 2

Negative T wave in Derivation III.

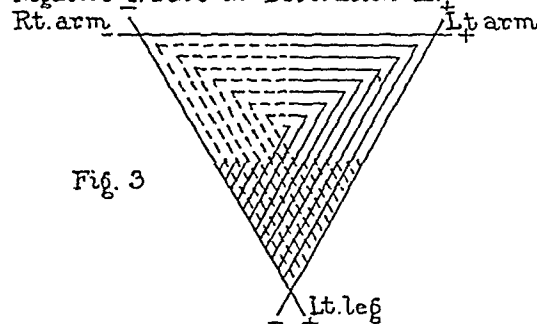


Fig. 3

Negative T wave in Derivations I and II.

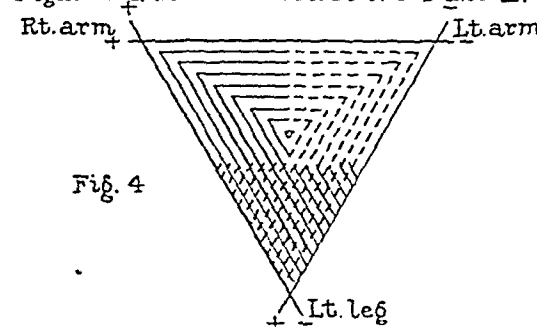


Fig. 4

Negative T wave in Derivations II and III

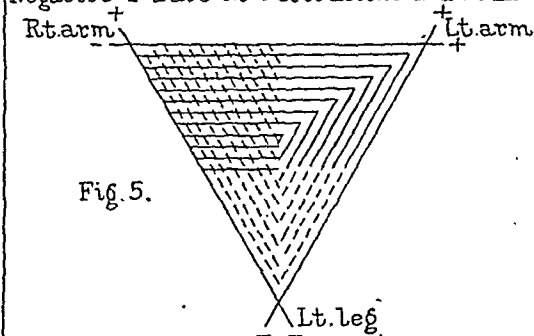


Fig. 5.

Negative T wave in Derivations I, II and III

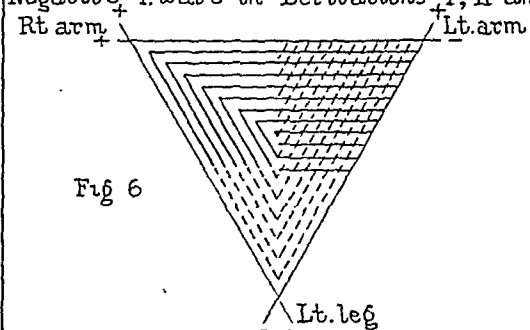


Fig. 6

Diffuse iso-electric state of heart if negative T wave in Derivation II occurred.

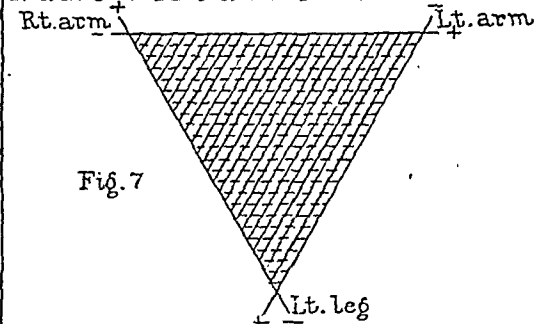


Fig. 7

Diffuse iso-electric state of heart if negative T wave in Derivations I and III occurred.

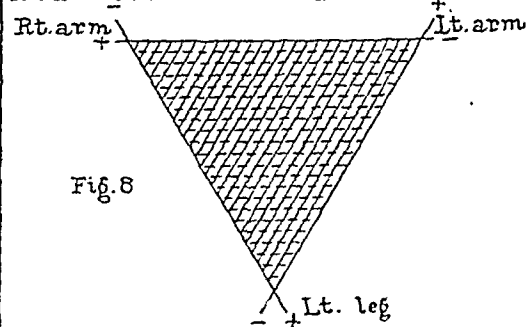


Fig. 8

changes in the electrocardiogram following ligation of any branch of the left coronary artery affected the *T* wave. A strongly positive to a markedly negative wave resulted fairly constantly with a slower return to positive or iso-electric. The negativity was usually observed within twenty-four hours after ligation and lasted for from three to four days. The duration seemed to bear a relationship to the size of the artery ligated. This work offers a tangible basis in directing attention to changes in the intrinsic blood supply of the heart, as evidenced by greater or lesser derangements of cardiac function. Morison has shown that blood-volume alterations may produce changes detectable in the electrocardiogram.

Increased general cellular function implies increased blood volume for the maintenance of normal tissue metabolism. In a specialized organ this augmentation is manifested by an increase in its function. In the heart increase in the blood volume beyond physiologic limits increases contraction. I refer particularly to increase of ventricular blood volume, since coronary volume is largely dependent on this factor. Because of impairment or disease of certain intrinsic channels of blood supply the affected muscle does not receive the requisite amount of blood properly to maintain function while the unaffected muscle demands greater blood volume for relatively more efficient contraction. This is an explanation for *T*-wave changes in isolated or combined derivations occurring permanently or temporarily.

#### THE ACTION OF THE CARDIAC NERVES ON *T*-WAVE NEGATIVITY.

Stimulation of the cardiac vagus has been shown to produce negativity of the *T* wave,<sup>5 29</sup> and the same observation is noted following stimulation of the left cervical sympathetic branches.<sup>28</sup>

A series of clinical observations were conducted on patients having negative *T* waves in isolated or combined derivations of their electrocardiograms. Following the initial tracing, pressure was applied in turn to the right vagus region in the neck, to the left vagus region and finally to the right eyeball (oculocardiac reflex) and the respective electrocardiograms obtained. In no instance was any change noted in the negative *T* wave or in the positive *T* wave of the unaffected derivations. Atropin (gr.  $\frac{1}{150}$ ) was then administered subcutaneously and records obtained every ten minutes for forty minutes. Again no effect on the *T* wave was noted. No change occurred following the subcutaneous administration of adrenalin (0.5 c.c. of a 1 to 1000 solution). These clinical procedures, however, are obviously not so accurate as direct experimental stimulation.

The present status of cardiac histopathology fails to explain many derangements of function. Histologic studies do not indicate why auricular fibrillation occurs in one heart and auricular



flutter in another. Disease of the cardiac conduction system is more definite histologically. Involvement below the auriculo-ventricular bundle is often associated with unquestionable intrinsic vascular changes.

There has been no adequate explanation of the occurrence of the negative *T* wave in isolated or combined derivations of the electrocardiogram. In the Mayo Clinic we have repeatedly observed the negative *T* wave in derivation 1, in derivation 3, in combined derivations 1 and 2, in combined derivations 2 and 3 and in combined derivations 1, 2 and 3. No instances of negativity in derivation 2 or in combined derivations 1 and 3 are recorded. This observation in 7000 electrocardiographic examinations eliminates the element of coincidence. There is a definite reason why these changes do not occur. Lewis states that the *T* wave is always upright in derivation 2 alone.

*T-wave Negativity in Derivation 1* (Fig. 2). Fig. 2 represents the arrangement of potential existing with this abnormality. The left arm becomes electronegative to the right while the other signs remain unchanged. The right upper zone instead of being electronegative becomes iso-electric while the left upper becomes electronegative to the apex. The occurrence of an iso-electric state in the right upper zone is a marked departure from the normal in that the area of primary electronegativity is altered.

*T-wave Negativity in Derivation 3* (Fig. 3). The left leg becomes electronegative to the left arm; the other derivations remain unchanged. The right upper zone remains electronegative with reference to the left upper. The apical zone becomes iso-electric. This distribution is but a slight deviation from normal in that the right upper zone remains electronegative.

*T-wave Negativity in Combined Derivations 1 and 2* (Fig. 4). The left arm becomes electronegative to the right arm and the left leg electronegative to the right arm. The third derivation remains unchanged. The left upper zone becomes electronegative to the right and the apical zone becomes iso-electric. This arrangement again deviates from the normal in altering the area of primary electronegativity; it is a lesser change in that the right upper zone becomes electropositive instead of iso-electric.

*T-wave Negativity in Combined Derivations 2 and 3* (Fig. 5). The left leg becomes electronegative to both arms. Derivation 1 remains unchanged. The apical zone becomes electronegative to the left upper while the right upper zone becomes iso-electric. This arrangement as in Derivation 1 is a marked change from normal in that the area of primary electronegativity becomes iso-electric.

*T-wave Negativity in Combined Derivations 1, 2 and 3* (Fig. 6). All derivations reverse their signs in relation to each other. The apical zone becomes electronegative to the right upper while the left upper zone becomes iso-electric. The upper zones assume

just the opposite relationship to each other that occurs in combined derivations 2 and 3. Here again the potential distribution is disturbed, the area of primary electronegativity becoming electropositive, approaching the changes accompanying *T*-wave negativity in combined derivations 1 and 2.

Figs. 7 and 8 illustrate the reason why *T*-wave negativity in derivation 2 and in combined derivations 1 and 3 does not occur. In derivation 2 the left leg would be electronegative to the right arm while the other derivations would remain unchanged. This distribution would imply a diffuse iso-electric cardiac state and would indicate that cardiac contraction had ceased. In combined derivations 1 and 3 the left arm would be electronegative to the right and the left leg to the left arm. This arrangement likewise would indicate a diffuse iso-electric state.

The greater the deviation from the normal potential distribution the greater the significance of the disorder responsible for the change. The greatest change occurring which is compatible with life is the iso-electric state occupying the right upper zone. Therefore *T*-wave negativity in derivation 1 and in combined derivations 2 and 3 should be associated generally with grave heart disease. Next in significance should be those distributions of potential rendering the left upper zone electronegative to the right and represented by *T*-wave negativity in combined derivations 1 and 2 and in combined derivations 1, 2 and 3.

In the distribution which most closely approximates normal the *T* wave is negative in derivation 3. In these cases the normal potential relationship of the right upper zone is maintained.

#### CLINICAL CONSIDERATION OF *T*-WAVE NEGATIVITY.

This study comprises 1106 cases of *T*-wave negativity in the electrocardiograms. One hundred and forty instances (12.6 per cent.) were noted in derivation 1, 688 (62.2 per cent.) in derivation 3, 62 (5.6 per cent.) in combined derivations 1 and 2, 171 (15.5 per cent.) in combined derivations 2 and 3, and 45 (4.1 per cent.) in combined derivations 1, 2 and 3. There was no instance of *T*-wave negativity in derivation 2 nor in combined derivations 1 and 3. Patients who had had digitalis within six weeks of the time of electrocardiographic examination were not included in this series.

#### *T*-WAVE NEGATIVITY AND VENTRICULAR PREPONDERANCE.

In the complete series about half (46.6 per cent.) of the electrocardiograms were associated with preponderance of the left ventricle. Preponderance of the right ventricle is evidenced by a negative *R* wave in derivation 1 and by a positive *R* wave in deri-

vation 3. In cases of preponderance of the left ventricle these changes are reversed. Right preponderance was infrequent (17.3 per cent.) and no unbalance was present in 36.1 per cent. of the electrocardiograms. Preponderance of the left ventricle occurred most often associated with *T*-wave negativity in derivation 1 and in combined derivations 1 and 2. No instance of right preponderance was noted with negativity in combined derivations 1, 2 and 3. These observations are summarized in Table I.

TABLE I.—T-WAVE NEGATIVITY AND VENTRICULAR PREPONDERANCE.

Derivation.	Total.	Left preponderance.	Percentage.	Right preponderance.	Percentage.	None.	Percentage.
1 . . . . .	140	120	85.7	5	3.6	15	10.7
3 . . . . .	688	274	39.8	132	19.2	282	41.0
1 and 2 . . . . .	62	52	83.9	4	6.4	6	9.7
2 and 3 . . . . .	171	43	25.2	51	29.8	77	45.0
1, 2 and 3 . . . . .	45	27	60.0	0	0	18	40.0
Total . . . . .	1106	516	46.6	192	17.3	398	36.1

TABLE II.—GRAVE HEART DISEASE ASSOCIATED WITH T-WAVE NEGATIVITY.

Derivation.	Total.	Arborization block.	Delayed auriculoventricular conduction.	Complete auriculoventricular dissociation.	Auricular fibrillation.	Auricular flutter.	Ventricular tachycardia.	Aortic disease.	Angina pectoris.
1 . . . . .	140	53	3	3	19	1	1	16	9
3 . . . . .	688	3	2	0	11	0	0	8	21
1 and 2 . . . . .	62	14	2	0	5	0	1	6	1
2 and 3 . . . . .	171	11	3	1	24	0	1	13	3
1, 2 and 3 . . . . .	45	3	3	0	11	0	0	8	2
Total . . . . .	1106	84	13	4	70	1	3	51	36

## ASSOCIATED DISEASES.

*T-wave Negativity in Derivation 1 (140 cases).* Myocardial degeneration associated with the hypertension group occurred with greatest frequency (38.6 per cent.) in the patients having *T*-wave

negativity in derivation 1 of their electrocardiograms. Three factors are probably responsible for the myocardial changes accompanying hypertension: (1) The cause or causes primarily responsible for the constitutional disorder; (2) the action on the myocardium of the retention products or of the intermediate products of incomplete metabolism or toxic agents resulting from imperfect renal or tissue function; and (3) the increased cardiac work, affecting largely the myocardium, resulting from the hypertension *per se* and the alterations in cardiovascular balance.

Chronic endocarditis occurred second in order of frequency (22.1 per cent. of the cases). The myocardial damage attending this disorder occurs concomitant with or secondary to the endocardial invasion (Table III). In no instance was the cardiac examination negative. In the majority of instances grave heart disease was present.

TABLE III.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATION 1.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
11 to 20	2	0	0	0	2	0	0	0	0	0	0	0
21 to 30	5	0	0	0	4	1	0	0	0	0	0	0
31 to 40	7	1	0	0	3	2	0	0	0	0	0	1
41 to 50	28	10	2	2	7	1	5	1	1	0	0	0
51 to 60	40	16	1	2	6	6	2	7	4	0	0	0
61 to 70	54	25	0	2	9	7	0	11	4	0	0	0
71 to 80	4	2	0	0	0	2	0	0	0	0	0	0
Total	140	54	3	6	31	19	7	19	9	0	0	1
Per cent	...	45			40.7			13.6		...	...	0.7

Fifty-three patients had arborization block, 3 had delayed auriculo-ventricular conduction, 3 had complete auriculoventricular dissociation, 19 had auricular fibrillation, 1 had auricular flutter and 1 had ventricular tachycardia. Sixteen patients had aortic disease. Nine had angina pectoris.

The high incidence of grave heart disease in this group verifies my previous statement regarding the potential distribution responsible for this negativity as being the greatest departure from normal. The right upper zone is iso-electric instead of electronegative.

*T-wave Negativity in Derivation 3 (688 Cases).* The relative frequency of *T-wave* negativity occurring in derivation 3 is at once apparent.

The myocardial degeneration secondary to exophthalmic goiter was the most frequently associated condition (19.2 per cent.). Myocardial damage due to exophthalmic goiter involves the cellular action of thyroxin<sup>17</sup> (thyroid active principle) on the myocardium<sup>27</sup> and the increased cardiac work accompanying the rise of the basal metabolic rate.

Chronic endocarditis occurred in 16.9 per cent. and chronic myocarditis in 14.8 per cent. By chronic myocarditis I refer to those cases of inflammatory origin in contradistinction to the cases of myocardial degeneration. Myocardial degeneration associated with the hypertension group occurred in only 10.8 per cent. of cases (Table IV).

TABLE IV.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATION 3.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
1 to 10	10	0	0	0	4	0	0	0	0	4	0	2
11 to 20	62	2	20	0	13	2	1	0	0	0	22	2
21 to 30	190	6	55	3	40	19	2	0	0	1	46	18
31 to 40	161	12	39	5	32	15	6	0	0	0	35	17
41 to 50	138	28	16	5	18	25	5	4	4	1	19	17
51 to 60	83	21	2	9	5	27	5	7	6	0	1	6
61 to 70	39	4	0	2	4	12	0	12	10	0	2	3
71 to 80	5	1	0	0	0	2	0	2	1	0	0	0
Total	688	74	132	24	116	102	19	25	21	6	125	65
Per cent.	...	33.4			34.4			3.7		0.9	18.2	9.4

Grave heart disease is relatively infrequent in this group; 3 patients had arborization block, 2 had delayed auriculoventricular conduction and 11 auricular fibrillation. Eight patients had aortic disease and 21 had angina pectoris. Twenty per cent. of the patients had no demonstrable evidence of organic heart disease. Of this number 40 per cent. had cardiac neurosis.

The relative infrequency of grave heart disease and the high

percentage of apparently normal hearts in this group are in marked contrast to the findings associated with *T*-wave negativity in derivation 1. These findings are in accord with the hypothetic significance of *T*-wave negativity in derivation 3. The potential distribution in this *T*-wave negativity is illustrated in Fig. 3. The right upper zone remains electronegative, the other zones reverse their potential, establishing an arrangement which does not materially depart from the normal.

The potential distribution occurring in such a relatively high percentage of apparently normal hearts and the frequent transient *T*-wave negativity in derivation 3 make functional myocardial fatigue a causative possibility in a certain number of cases at least.

*T-wave Negativity in Combined Derivations 1 and 2 (62 Cases).* Myocardial degeneration associated with the hypertension group occurred in half (50 per cent.) of the patients having *T*-wave negativity in combined derivations 1 and 2. Chronic endocarditis was present in 20.9 per cent. of the cases. In no instance was the cardiac examination negative. These findings are summarized in Table V. About half (46.7 per cent.) of the cases were associated with grave heart disease. Fourteen patients had arborization block, 2 had delayed auriculoventricular conduction, 5 had auricular fibrillation and 1 had ventricular tachycardia. Six patients had aortic disease and 1 of these had an aortic aneurysm. One patient had angina pectoris.

TABLE V.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATIONS 1 AND 2.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
21 to 30	7	0	0	0	6	1	0	0	0	0	0	0
31 to 40	5	3	0	0	2	0	0	0	0	0	0	0
41 to 50	13	7	0	1	1	3	0	0	0	0	0	1
51 to 60	20	14	1	0	2	1	1	1	1	0	0	0
61 to 70	15	7	0	1	2	1	1	3	0	0	0	0
71 to 80	2	0	0	0	0	1	0	1	0	0	0	0
Total	62	31	1	2	13	7	2	5	1	0	0	1
Per cent.	...	54.8			35.5			8.1		...	...	1.6

Reference to the potential distribution responsible for *T*-wave negativity in this derivation combination (Fig. 4) shows that the normal potential (electronegativity) of the right upper zone is disturbed. The left upper zone becomes electronegative to the right upper. Although this is a distinct departure from normal it is less marked than those states in which the right upper zone becomes iso-electric.

*T-wave Negativity in Combined Derivations 2 and 3 (171 Cases).* Chronic endocarditis occurred with greatest frequency (26.9 per cent.) in those patients having *T*-wave negativity in combined derivations 2 and 3. In order of frequency followed myocardial degeneration associated with exophthalmic goiter (21 per cent.), chronic myocarditis (17.5 per cent.), and myocardial degeneration associated with the hypertension group (15.8 per cent.).

A large percentage of the patients had grave heart disease. Eleven patients had arborization block, 3 had delayed auriculo-ventricular conduction, 1 had complete auriculoventricular dissociation, 24 had auricular fibrillation and 1 ventricular tachycardia. Thirteen patients had aortic disease and 3 had angina pectoris. In 9 cases the cardiac examination was negative. These observations are illustrated in Table VI.

TABLE VI.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATIONS 2 AND 3.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
11 to 20	12	1	4	0	5	2	0	0	0	0	0	0
21 to 30	45	1	13	0	16	6	1	0	0	0	5	2
31 to 40	39	4	10	1	14	4	0	0	0	1	3	3
41 to 50	34	5	8	3	6	8	1	0	0	2	1	0
51 to 60	28	10	0	1	4	8	0	4	2	0	0	1
61 to 70	12	5	1	0	1	2	1	2	1	0	0	0
71 to 80	1	1	0	0	0	0	0	0	0	0	0	0
Total	171	27	36	5	46	30	3	6	3	3	9	6
Per cent.	...	39.8			46.2			3.5		1.7	5.3	3.5

Again the reader is referred to Fig. 5, which illustrates the potential distribution in *T*-wave negativity in this derivation combination. The similarity to the potential arrangement attending *T*-wave negativity in derivation 1 may be noted.

*T-wave Negativity in Combined Derivations 1, 2 and 3 (45 Cases).* *T*-wave negativity in derivations 1, 2 and 3 constituted the smallest group, comprising only 4.1 per cent. of the total series.

Myocardial degeneration associated with the hypertension group occurred most often (35.5 per cent.), and in order of occurrence chronic endocarditis (24.4 per cent.) and chronic myocarditis (20 per cent.). Every patient in this group had definite clinical evidence of heart disease (Table VII).

TABLE VII.—ASSOCIATED DISEASES. T-WAVE NEGATIVITY IN DERIVATIONS 1, 2 AND 3.

Decade.	Total.	Degenerative processes.			Infections.			Local nutritional disturbances.		Congenital heart disease.	No cardiac findings.	Inconclusive cardiac findings.
		Hypertension with and without clinical nephritis.	Exophthalmic goiter.	Adenomas with hyperthyroidism.	Chronic endocarditis.	Chronic myocarditis.	Syphilis.	Arteriosclerosis.	Angina pectoris.			
11 to 20	1	0	0	0	1	0	0	0	0	0	0	0
21 to 30	4	0	0	0	2	1	0	0	0	1	0	0
31 to 40	7	1	0	0	4	1	1	0	0	0	0	0
41 to 50	9	2	1	2	0	3	1	0	0	0	0	0
51 to 60	12	8	0	0	2	0	0	2	1	0	0	0
61 to 70	12	5	0	0	2	4	0	1	1	0	0	0
Total	45	16	1	2	11	9	2	3	2	1	0	0
Per cent.	...	42.2			48.8			6.6		2.2		

Three of the patients with the graver forms of heart disease had arborization block, 3 delayed auriculoventricular conduction and 11 auricular fibrillation. Eight patients had aortic disease and 2 had angina pectoris. If the potential distribution in this disorder is taken into consideration the apical zone will be found electronegative to the right upper while the left upper zone will be iso-electric (Fig. 6). This arrangement is similar to that attending *T*-wave negativity in combined derivations 1 and 2 in that the right upper zone is electropositive. It likewise is a distinct deviation from normal.



TABLE VIII.—ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH T-WAVE NEGATIVITY.

Derivation.	Total.	T-wave negativity unattended.	Sinus arrhythmia.	Auricular premature contractions.	Auricular and nodal premature contractions.	Ventricular premature contractions.	Ventricular and nodal premature contractions.	Ventricular premature contractions and sinus arrhythmia.	Auricular fibrillation and ventricular premature contractions.	Auricular fibrillation and aberrant Q R S complexes in isolated derivations.	Auricular fibrillation and aberrant Q R S complexes in isolated derivations and ventricular premature contractions.	Abortization block.	Abortization block and auricular premature contractions.	Abortization block and auricular premature contractions.	Abortization block and delayed auriculoventricular conduction.	Aberrant Q R S complexes in isolated derivations.	Aberrant Q R S complexes in isolated derivations and auricular premature contractions.	Aberrant Q R S complexes in isolated derivations and ventricular premature contractions.	Delayed auriculoventricular conduction.	Delayed auriculoventricular conduction and sinus arrhythmia.	Delayed auriculoventricular conduction, aberrant Q R S complexes in isolated derivations and ventricular premature contractions.	Complete auriculoventricular dissociation.	Auricular flutter.	Nodal tachycardia.	Ventricular tachycardia.	
1 . . .	140	41	0	2	0	6	0	0	8	1	0	36	3	8	4	2	1	2	1	0	0	3	1	1	1	
3 . . .	688	550	24	14	1	4	1	0	17	0	1	10	0	2	0	0	0	1	0	0	0	0	0	1	1	
1 and 2 . .	62	32	0	2	0	1	0	0	3	0	0	11	0	1	1	2	0	0	1	0	0	0	0	0	1	
2 and 3 . .	171	112	1	5	0	1	0	0	20	0	0	4	0	5	1	1	0	0	1	1	0	1	0	1	1	
1, 2 and 3 .	45	21	0	2	0	0	0	0	8	0	0	2	0	1	0	0	0	0	2	0	1	0	0	0	0	
Total . .	1106	756	25	25	1	17	6	1	67	2	1	63	3	17	6	4	16	1	3	5	1	1	4	1	1	3

TABLE IX.—VALVULAR DISEASE ASSOCIATED WITH T-WAVE NEGATIVITY.

Decade.	Total.	Mitral disease.						Aortic disease.						
		Mitral regurgitation.	Mitral stenosis.	Double mitral lesion.	Mitral and polyvalvular regurgitation.	Double mitral lesion and aortic regurgitation.	Mitral stenosis and aortic regurgitation.	Aortic regurgitation.	Aortic stenosis.	Double aortic lesion.	Aortitis.	Aortic regurgitation and aortitis.	Aortic and polyvalvular regurgitation.	Aortic and mitral regurgitation.
1 . . . . .	37	16	0	2	1	2	0	3	2	2 <sup>1</sup>	2 <sup>2</sup>	5 <sup>2</sup>	2 <sup>1</sup>	0
3 . . . . .	122	64	27	7	0	2	0	10 <sup>3</sup>	1	2	1 <sup>1</sup>	2 <sup>2</sup>	0	6
1 and 2 . . . .	14	5	0	1	1	1	1	2	1	2 <sup>1</sup>	0	0	0	0
2 and 3 . . . .	49	22	7	5	2	0	0	4 <sup>1</sup>	1	3	2 <sup>1</sup>	1 <sup>1</sup>	2	0
1, 2 and 3 . . .	12	4	0	0	0	0	0	3	0	2	0	3 <sup>1</sup>	0	0
Total . . . . .	234	111	34	15	4	5	1	22	5	11	5	11	4	6

<sup>1</sup> One patient in this group had syphilitic lesions.<sup>2</sup> Two patients in this group had syphilitic lesions.<sup>3</sup> Three patients in this group had syphilitic lesions.

## CARDIAC MORTALITY AND T-WAVE NEGATIVITY.

*T-wave Negativity in Derivation 1.* Information has been received concerning 117 patients having T-wave negativity in derivation 1 of their electrocardiograms. Seventy-eight (66.6 per cent.) have died from heart disease during a period of four and a half years (Table X). The mortality in every decade is high; the lowest

TABLE X.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN DERIVATION 1.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
11 to 20 . . . .	2	2	2	0	1	50.0	1	0	1	0	0
21 to 30 . . . .	5	5	3	2	3	60.0	2	0	0	2	0
31 to 40 . . . .	7	6	6	0	4	66.6	2	1	1	0	0
41 to 50 . . . .	28	24	13	11	11	45.8	11	2	6	3	0
51 to 60 . . . .	40	32	22	10	21	65.6	9	2	5	2	0
61 to 70 . . . .	54	44	33	11	35	79.5	8	5	2	1	0
71 to 80 . . . .	4	4	4	0	3	75.0	0	0	0	0	0
Total . . . . .	140	117	83	34	78	66.6	33	10	15	8	0

percentage (45.8) occurred between the ages of forty-one and fifty. Thirty-three patients are alive and 10 of these report their conditions worse, 15 are improved and 8 are unchanged. None of the patients was without cardiac complaints.

The high cardiac mortality in this group is in accord with the hypothetic and clinical significance, previously emphasized, which attends this *T*-wave negativity. To prevent misunderstanding it may be stated that the negative *T* wave *per se* is only the manifestation of serious underlying myocardial disorder. Changes in cardiac function affecting contraction preponderance resulting from organic or functional myocardial fatigue alter electropotential, which produces *T*-wave negativity.

*T-wave Negativity in Derivation 3.* Information has been received concerning 487 patients having *T*-wave negativity in derivation 3 of their electrocardiograms. Forty-six (9.4 per cent.) have died from heart disease during a period of four and a half years. The data are summarized in Table XI. This relatively low cardiac

TABLE XI.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN DERIVATION 3.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
1 to 10 . . .	10	8	3	5	2	25.0	5	0	3	2	3
11 to 20 . . .	62	42	9	33	2	4.7	40	7	20	13	17
21 to 30 . . .	190	139	22	117	5	3.5	127	30	53	44	37
31 to 40 . . .	161	113	27	86	9	7.9	99	23	33	43	25
41 to 50 . . .	138	89	24	65	9	10.1	78	18	30	30	20
51 to 60 . . .	83	68	37	31	13	19.1	53	13	18	22	3
61 to 70 . . .	39	24	15	9	5	20.8	16	6	3	7	1
71 to 80 . . .	5	4	3	1	1	25.0	2	0	1	1	0
Total . . .	688	487	140	347	46	9.4	420	97	161	162	106

TABLE XII.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN COMBINED DERIVATIONS 1 AND 2

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
21 to 30 . . .	7	5	5	0	4	80.0	1	0	0	1	0
31 to 40 . . .	5	3	3	0	3	100.0	0	0	0	0	0
41 to 50 . . .	13	11	9	2	7	63.6	3	0	2	1	1
51 to 60 . . .	20	19	13	6	12	63.1	7	1	5	1	0
61 to 70 . . .	15	12	8	4	7	58.3	5	0	5	0	0
71 to 80 . . .	2	2	1	1	2	100.0	0	0	0	0	0
Total . . .	62	52	39	13	35	67.3	16	1	12	3	1

mortality is sharply contrasted with the mortality of the foregoing group. It is in agreement, however, with the hypothetic and clinical significance accorded *T*-wave negativity in derivation 3.

The potential distribution producing this negativity is but a slight departure from normal. Four hundred and twenty patients are alive, 97 report their conditions worse, 161 are improved and 162 are unchanged. One hundred six patients report no cardiac complaints.

*T-wave Negativity in Combined Derivations 1 and 2.* Of the 52 patients having *T-wave* negativity in combined derivations 1 and 2 concerning whom we have heard, 35 (67.3 per cent.) have died from heart disease during four and a half years. This mortality is greater than was anticipated in that the potential distribution resulting in this *T-wave* negativity was not the greatest departure from normal. In Fig. 4, in which the potential distribution is represented, the right upper zone becomes electropositive to the left instead of electronegative as in the normal, but this is a lesser departure than iso-electric. The fact that the group is relatively small may be a factor in obtaining a high cardiac mortality. Sixteen patients are alive, 1 reports his condition worse, 12 are improved and 3 are unchanged. Only 1 patient reports no cardiac complaint.

*T-wave Negativity in Combined Derivations 2 and 3.* We have learned of the condition of 135 patients having *T-wave* negativity in combined derivations 2 and 3. Thirty-five (25.9 per cent.) have died from heart disease during a period of four and a half years (Table XIII). In contradistinction to the foregoing group the mortality was lower than expected from a hypothetical consideration of potential distribution and associated heart disease. A possible explanation for this discrepancy rests in the fact that 23.3 per cent. of the patients were examined during the last year of the series, and the time element, therefore, is too short to embrace a true mortality average. Eighty-eight patients are alive; 25 report their conditions worse, 37 are improved and 26 are unchanged. Sixteen patients report no cardiac complaints; 7 of these had had thyroidectomies for hyperthyroidism and were cured.

TABLE XIII.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN COMBINED DERIVATIONS 2 AND 3.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
11 to 20 . . .	12	9	0	9	0	0	9	2	4	3	2
21 to 30 . . .	45	34	11	23	9	26.4	22	7	10	5	6
31 to 40 . . .	39	32	9	23	5	15.6	24	7	9	8	7
41 to 50 . . .	34	27	16	11	8	29.6	17	4	7	6	1
51 to 60 . . .	28	20	15	5	6	30.0	12	2	7	3	0
61 to 70 . . .	12	12	9	3	6	50.0	4	3	0	1	0
71 to 80 . . .	1	1	1	0	1	100.0	0	0	0	0	0
Total . . .	171	135	61	74	35	25.9	88	25	37	26	16

*T-wave Negativity in Combined Derivations 1, 2 and 3.* Patients having *T-wave* negativity in all derivations comprised a relatively small group. Nineteen of the 38 (50 per cent.) on whom we have had reports have died from heart disease during four and a half years (Table XIV). This mortality agrees fairly well with hypo-

TABLE XIV.—CARDIAC MORTALITY. T-WAVE NEGATIVITY IN COMBINED DERIVATIONS 1, 2 AND 3.

Decade.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
11 to 20 . . .	1	1	0	1	1	100.0	0	0	0	0	0
21 to 30 . . .	4	2	2	0	1	50.0	1	0	1	0	0
31 to 40 . . .	7	5	3	2	2	40.0	2	0	1	1	0
41 to 50 . . .	9	9	6	3	1	11.1	6	0	5	1	0
51 to 60 . . .	12	10	10	0	9	90.0	1	1	0	0	0
61 to 70 . . .	12	11	8	3	5	45.5	5	4	1	0	0
Total . . .	45	38	29	9	19	50.0	15	5	8	2	0

thetic considerations of potential distribution and associated grave heart disease (Fig. 6). Fifteen patients are alive, 5 report their conditions worse, 8 are improved and 2 are unchanged. No patient was without cardiac complaint.

In the complete series of *T-wave* negativity, regardless of derivation grouping, information has been received concerning 829 patients. Two hundred and thirteen (25.6 per cent.) have died from heart disease (Table XV).

TABLE XV.—CARDIAC MORTALITY IN COMPLETE SERIES.

Derivation.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
1 . . . . .	140	117	83	34	78	66.6	33	10	15	8	0
2 . . . . .	688	487	140	347	46	9.4	420	97	161	162	106
1 and 2 . . .	62	52	39	13	35	67.3	16	1	12	3	1
2 and 3 . . .	171	135	61	74	35	25.9	88	25	37	26	16
1, 2 and 3 . .	45	38	29	9	19	50.0	15	5	8	2	0
Total . . .	1106	829	352	477	213	25.6	572	138	233	201	123

A group of cases was compiled including those cases in which there was *T-wave* negativity without other electrocardiographic abnormalities except ventricular preponderance. This was done with the idea of excluding disorders of cardiac action known in themselves materially to influence cardiac mortality, especially

auricular fibrillation and flutter, ventricular tachycardia, delayed auriculoventricular conduction, complete auriculoventricular dissociation and arborization block. Of the 559 patients in this group of whose condition we have learned, 92 (16.4 per cent.) have died from heart disease (Table XVI). The cardiac mortality in this group is 9.2 per cent. less than that of the complete series.

TABLE XVI.—CARDIAC MORTALITY. T-WAVE NEGATIVITY WITHOUT OTHER ELECTROCARDIOGRAPHIC ABNORMALITIES.

Derivation.	Total.	Patients heard from.	Males.	Females.	Cardiac deaths.	Percentage.	Living.	Worse.	Improved.	Unchanged.	No cardiac complaints.
1 . . . . .	41	32	21	11	17	53.1	13	4	7	2	0
3 . . . . .	550	394	86	308	33	8.3	349	76	132	141	83
1 and 2 . . . .	32	29	23	6	17	58.6	12	1	8	3	1
2 and 3 . . . .	112	86	33	53	17	19.7	61	18	28	15	14
1, 2 and 3 . . .	21	18	15	3	8	44.4	7	2	4	1	0
Total . . . . .	756	559	178	381	92	16.4	442	101	179	162	98

### CONCLUSIONS.

1. The ventricular complexes of the electrocardiogram are the expressions of two distinct processes, impulse conduction and muscle contraction.

2. The *T* wave is the expression of preponderance of contraction on one side of the line of equipotential (Eyster and Meek).

3. *T*-wave negativity results from alteration in potential distribution from changes in contraction preponderance. Changes in contraction preponderance may result from changes in blood volume and from organic or functional myocardial fatigue.

4. The occurrence of *T*-wave negativity in certain isolated and combined derivations of the electrocardiogram bears a fairly definite relationship to degrees of cardiac damage.

5. The significance of *T*-wave negativity in this series as evidence of heart disease in order of gravity is in (1) combined derivations 1 and 2; (2) derivation 1; (3) combined derivations 1, 2 and 3; (4) combined derivations 2 and 3; and (5) derivation 3.

6. *T*-wave negativity in derivation 2 and in combined derivations 1 and 3 has not been observed in the Mayo Clinic and according to the hypothesis cannot exist. Such negativity would indicate a diffuse iso-electric state of the heart which would mean cardiac standstill.

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## ILEAL REGURGITATION, NERVES AND DIET IN THE CHRONIC INTESTINAL INVALID.\*

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I. INTRODUCTION. Since 1566<sup>1</sup> it has been known there is a structure called the ileocecal valve, and it has been known since 1570<sup>2</sup> that the valvular function of this structure is to prevent the regurgitation of feces into the small intestine. Furthermore, it has been known for ninety-eight years<sup>3</sup> that the active muscular sphincteric function of the mechanism at the distal end of the ileum is to moderate the flow of the contents of the small intestine into the colon.

Actual incompetence of the ileocecal valve was first produced experimentally in 1586.<sup>4</sup> This condition has been recognized as a clinical entity for twenty-three years,<sup>5</sup> and its existence was demonstrated in the human by the bismuth-roentgen method at least eighteen years ago.<sup>6</sup> Yet Cole,<sup>6</sup> writing six years ago, was obliged to bemoan the fact that he was unable to arouse any interest in this subject, even on asking if symptoms might be expected, should a patient be fed colonic contents. Cole, Case and other authorities in roentgen work have recognized a correlation in the degree of ileal regurgitation and the severity of the symptoms complained of by

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the patient, and the probable causative connection between ileal regurgitation and many cases of ileal stasis has frequently been pointed out.

Case,<sup>7</sup> in 1913, reported ileal regurgitation in over 16 per cent. of 1500 consecutive gastro-enterological cases. Cole<sup>8</sup> believes that one might expect to find, with modern technic, perhaps 30 per cent. of ileal regurgitation. Baetjer<sup>9</sup> has stated that it is possible to find as high as 50 per cent. of ileal regurgitation by including every case in which a little of the barium enema can be demonstrated to have entered the terminal ileum. Yet even today almost no one can be found who will take more than the most casual interest in this subject in other than a purely academic manner.

If 30 per cent. of all patients coming for gastro-intestinal examination had regurgitation of food into the mouth all the time, someone would soon have to take interest. In the same way if 30 per cent. of all gastro-intestinal patients suffered from chronic rectal incompetence something would certainly get done about it. Yet just because the junction between the ileum and the colon is unable to cause external annoyance to the patient or his friends, nothing gets done about it. It is easy to create a furor about the appendix or a gall-stone but not about the ileocecal mechanism. Why? Possibly because anatomies pass it over with a few lines of small type, medical schools pass it by in parenthesis and students devote their time to something more obvious. Under these circumstances it is scarcely to be wondered at if the victim of ileal regurgitation turns in disgust from physicians who remain ignorant, more than four hundred years after its discovery, concerning an important anatomic and physiologic structure in order to obtain perhaps a little alleviation of symptoms at the hands of some cult not in the regular profession.

The term ileal regurgitation as here used includes not only regurgitation into the ileum resulting from incompetence of the actual ileocecal protective mechanism but also the condition produced surgically by operative removal of the ileocecal area of the intestine; there is thus produced the same condition of continuity between the colon and small intestine. Two such surgically produced cases of regurgitation are included in the present study. For purposes of treatment both these groups of cases are in the same class on account of their lack of a break in continuity between the large and small intestine.

The objects of this paper are as follows:

1. To draw attention to the fact that too little attention is being devoted to ileal regurgitation, a pathologic condition which is a fact and not a theory.
2. To point out the ease and certainty with which the presence of this condition may be determined.

3. To present for consideration a new diagnostic sign of ileal regurgitation which is at least suggestive in value.

4. To indicate the remarkable frequency of ileal regurgitation in the class of cases referred to as chronic intestinal invalids.

5. To indicate the almost constant coexistence of ileal regurgitation and various forms of excessive nervous irritability.

6. To outline a non-surgical method of treatment which has given a reasonable degree of satisfaction.

7. To record the results of such treatment in a consecutive series of fifty chronic intestinal invalids.

II. DIAGNOSIS. (a) Hertz,<sup>5</sup> in 1897, reported a clinical sign the presence of which was considered by him to indicate the existence of ileal regurgitation. Treatment carried out by him on the assumption of the existence of regurgitation apparently gave satisfactory results. His diagnostic procedure was as follows: One hand is pressed deep across the middle of the ascending colon to block possible distal expulsion of gas in the cecum. Downward pressure with the other hand in the direction of the pole of the cecum will then, if regurgitation exists, result in coarse crepitation and perhaps a gurgling noise as the cecal gas is forced back into the ileum.

(b) Gas is not usually present in the small intestine. The presence of generalized gas throughout the abdomen suggests a deficient ileocecal mechanism.

(c) A cecum and ascending colon dilated with gas combined with a spastic descending colon frequently accompany ileal regurgitation.

(d) In the presence of this condition the hepatic flexure and the sigmoid loop are frequently distended by gas.

(e) A generalized yellowish discoloration of the skin, especially in the distribution areas affected by Addison's disease, is usual.

(f) The eye sign is positive. By the eye sign is indicated a marked dirty discoloration of the whole of both eye sockets. This discoloration is not like other more or less limited discolorations about the eyes with which the writer is familiar. This sign is suggestive, not pathognomonic. It is practically always present, varying in degree with the intensity and duration of the ileal regurgitation. It may be present in the absence of such regurgitation. Should this be the case, however, treatment, as for ileal regurgitation, will cause a gradual disappearance of the sign in the same manner, but more rapidly than is the case when ileal regurgitation has been demonstrated to exist.

(g) The usual complaints of the patient with ileal regurgitation are abdominal pain of various sorts, intestinal gas, constipation and nerves.

The pain complained of may be a slight general abdominal discomfort or it may be associated with the presence of gas, particularly in the cecum, hepatic flexure or sigmoid loop, more rarely in the splenic flexure. A second type of pain in these cases is a high central

epigastric pain which often becomes confused with that of gastric ulcer; this particular type of pain is frequently relieved by increase of the costal angle through appropriate developmental exercises. A third characteristic type of pain is a transverse soreness of the abdomen, apparently definitely related to the existence of a spastic transverse colon. A fourth type of pain is that due to distress of the heart following pressure from excessive gas in the stomach, resembling in character the heart pain complained of by the typical neurocardiac asthenic patient.

Constipation is almost universal, being usually of the spastic variety, which in the majority of cases shows definite improvement under the administration of atropine.

(h) Diagnosis is absolute by roentgen examination. The presence of a majority of the above signs or symptoms should be sufficient to indicate the necessity for a thorough roentgen examination of the gastro-intestinal tract. This will usually yield more or less negative results if the examination stops short of the administration of an opaque enema, although the previous examination is of value in determining whether the colon is spastic or whether it has become atonic, the latter condition very possibly a later exhaustion stage following the spastic state.

Judging from the relative infrequency with which patients referred to me—often after gastro-intestinal examination by competent roentgenologists—have previously been given an enema, the opaque enema is considered unnecessary; or possibly this omission occurs because, unless it is habitual routine, the administration of the opaque enema is distasteful. There is no doubt, however, that the opaque enema is the most valuable single procedure available today in the study of conditions existing within the colon and at the ileocecal juncture, especially with fluoroscopic observation of the withdrawal or expulsion of the enema at the completion of the usual examination.

In all of the fifty cases here reported the administration of the opaque enema was followed by a study of the filled colon; the enema was then withdrawn, the entire procedure being followed fluoroscopically. Much colon physiology is learned by watching the colon empty itself. If the terminal ileum is filled by regurgitation it usually remains filled until the entire colon empties from cecum to ampulla. The ileal contents thereafter may or may not be seen to follow the course of the colonic contents from cecum to ampulla, the whole distance occasionally being traversed by a block of opaque substance previously in the ileum in the space of a comparatively few seconds. To see a long, ptotic, festooned, loosely attached, M-shaped colon suddenly transform itself into a short omega style colon without evident excess of length anywhere, in order apparently to facilitate the smooth and rapid passage of large blocks of colonic contents, is to get new ideas on whether or not to do frequent fixa-

tion of the colon. Fluoroscopic study of the withdrawal of the opaque enema is certainly too little practised. There is no substitute for this procedure, which if properly carried out is rapid and satisfactory both to the patient and to the observer.

III. FREQUENCY OF ILEAL REGURGITATION On the basis of the observations by Case, Cole, Baetjer and others it would seem that ileal regurgitation may be expected in 20 to 30 per cent. of any series of gastro-intestinal cases. Therefore, if one finds a frequency higher than 50 per cent. in any consecutive series of cases it must be considered distinctly unusual.

In the series of 50 consecutive chronic intestinal invalids upon which this paper is based the existence of ileal regurgitation was demonstrated in 80 per cent. of the cases. Such a high frequency of ileal regurgitation is, to say the least, surprising and calls if possible for explanation.

The technic employed was identical. All observations were made by both Dr. L. B. Morrison and the writer. A large rectal tube was used. The enema was allowed to flow in until the cecum was barely well filled. The flow of the enema was then checked before any evidence of undue distention occurred. No manipulation was indulged in until it had been determined if the barium suspension would be carried back into the ileum by antiperistalsis. Occasionally a half-minute or so would elapse before antiperistalsis became active enough to produce visible ileal regurgitation. Only cases in which antiperistalsis by itself and without external pressure carried the barium back into the ileum were recorded as having regurgitation. On the other hand it may be stated that it was rather unusual to find a case in which factors other than antiperistalsis did cause regurgitation, possibly in view of the precaution taken against overdistention of the cecum. Cases showing regurgitation after changes in position or the strains incident to evacuation of the bowels were not classed as having regurgitation.

After fluoroscopy of the filled colon and the taking of plates as necessary the receptacle containing the enema was dropped to the floor and the emptying of the colon was studied fluoroscopically. This procedure yielded much information concerning colon physiology and cannot be too highly recommended to those interested in gastro-enterology.

In view of the above precautions there is little doubt about the facts in relation to this 80 per cent. frequency of ileal regurgitation in the group of cases studied.

Consequently, it seems necessary to look for some underlying reason for such frequency in connection with the condition of the patients themselves. The inference is that this astonishingly high frequency of regurgitation found in these cases may be considered as a factor worthy of attention in the carrying out of any treatment directed toward improving the general health of the patients presenting this condition.

IV. FREQUENCY OF THE EXISTENCE OF NERVES. The complaint of nerves, sometimes of most bizarre type, seems almost constant in the chronic intestinal invalid. In fact, there was but one case in fifty which did not complain of some form of increased nervous irritability or tension. The frequency of this complaint in the series of cases under consideration is therefore 98 per cent. One example is sufficient to indicate the curious manifestations of nerves which these patients may present.

Mr. R. P.; sculptor, white, aged thirty-five years, single, height six feet, weight 205 pounds, with good habits, brought up on a Western ranch, was first seen October 7, 1919.

*Family History.* Father died of cancer of the rectum at sixty-six years of age, family history otherwise negative.

*Personal History.* Patient lived always in the open, mostly on horseback, until the age of twenty-two. He could always keep up with the others in doing heavy, physical labor, but he "always felt as though he weighed a ton," and never liked exercise, feeling that he always expended excessive energy for the results produced. Patient had measles at eight, mumps severely at fourteen and scarlet fever at sixteen. Otherwise the early history was negative. Patient began to worry about the future at twelve to fourteen years of age, probably on account of the straightened circumstances of the family. He always had a desperate desire to study art, and has been active in sculpture for the last fifteen years.

*Present Illness.* Nervous, worried easily, gets along, but uses up excessive energy. Has never collapsed, but frequently has difficulty in controlling his temper, and after the close of any strenuous session with students or others is likely to get weepy. Has fainted four times, the last two times after being waked up at night by abdominal cramps. These occasions were one year ago and two nights before first coming for advice. On the latter occasion patient woke up with abdominal cramps, promptly fainted and was not normal for an hour.

Patient complains of a "woozy feeling in the lower jaw" and "a hot spot on the crown of the head, roughly circular in shape, about three inches in diameter, approximately in the position of a priest's tonsure." This hot spot has been present for many months and can be accurately outlined with the finger. The existence of this hot spot has seemed parallel to a decreased efficiency in the power of expression of thought and other forms of mental concentration. Patient has suffered intermittently from coxalgia, this condition having been almost constant for the past few months.

*Physical Examination.* Physical examination in general negative, the patient being tall, with a large frame and very sloping shoulders. The musculature is at present deficient. Posture fair. Skin negative except for some discoloration, and numerous pimples on the back. Pulse, 65; blood-pressure, 140-90. Eye sign positive.

Gastro-intestinal roentgen examination, beginning October 9, showed a sluggish stomach, with slight pyloric spasm, normal duodenum and normally shaped colon. The ileocecal valve was incompetent, the last one or two feet of ileum remaining filled after the evacuation of the enema. The ileum seemed sluggish in action. To promote possible action the patient was given a half glass of water to drink. Twenty to thirty seconds afterward the terminal ileum was suddenly and completely evacuated, after two definite and very vigorous forward and backward movements of the block of opaque substance contained in the ileum. It was very striking to observe this sudden activity of the ileum apparently as a result of the ingestion of a half glass of water.\*

*Treatment.* Active treatment, chiefly by diet and exercise, commenced on October 11, 1919. Improvement was rapid and continuous. On October 25 the patient reported that the hot spot on the back of his head had been gone for twenty-four hours and that his head was clearer. On October 29 the patient stated there had been no return of the hot spot and that his head was perfectly clear. He said that he had done a hard day's work, during which he had not felt tired as usual. He considered himself cured of his nerves and had no more coxalgia. On November 5 the patient reported that he was "feeling fine." He stated that he was convinced that an excessive use of food had been a serious factor in his condition and that he would hereafter be distinctly temperate both in food and candy. He said that he was very pleased because he had been able to do a real piece of constructive writing for a report which had been accepted as a unanimous opinion by the committee on which he was working. He also stated that this was the first time for nearly two years that he had felt his head to be in good order for intellectual purposes. On December 3 the patient wrote that he was "too well to waste time or money on doctoring."

V. RELATION OF ILEAL REGURGITATION TO NERVES. Since nerves of some kind were present in 98 per cent. of the fifty cases and regurgitation was present in only 80 per cent. the nerves cannot be said to be always secondary to ileal regurgitation. A study of the 20 per cent. of cases in the series free from ileal regurgitation gives the following results.

The ten chronic intestinal invalids with nerves but with normal ileocecal mechanism were divided between the herbivorous and carnivorous human types<sup>10</sup> in the proportion of 6 to 4. In the herbivorous group, however, one-half the cases had a definite organic lesion, as a possible cause for nervousness. In the remaining herbivorous cases, and in all of the four carnivorous cases, there was no obvious cause for nerves outside the neuropsychiatric sphere. It is probable that overwork, mental worries and fatigue were

\* This observation has been repeated, and the procedure outlined has been found useful on numerous occasions since the above was written.

factors in all cases. It is of interest, however, that none of the carnivorous cases had an organic factor. This is directly in line with the results of a study reported by Hodskins<sup>11</sup> concerning human type and the etiology of epilepsy following suggestions by the writer.

As a result of the above it seems probable that ileal regurgitation acts, if at all, only as a precipitating factor, which promotes, possibly through chemical metabolic means, nervous irritability. This is the more probable, in view of the fact that various small forms of superficial nervous irritability disappear rapidly after the application of a diet directed toward preventing the usual undesirable symptoms of ileal regurgitation, parallel with the improvement noted in the functioning of the digestive system. After this comparatively rapid primary improvement, however, there then remains the fundamental irritability of the nervous system, varying with the individual, to be combated by appropriate therapeutic procedures.

VI. TREATMENT. Treatment is divided into the early, intermediate and late stages of convalescence. In general, during the early stage, the objectives are external and internal rest, varied by carefully controlled periods of exercise. This means that after perhaps a few days of complete bodily rest, if this be deemed essential, the patient, if as usual ambulatory, takes up again his daily life, but with the work periods broken as nearly as possible by five-minute rests every half-hour during the day. This specification is based upon the principle that rest from fatigue is effective inversely according to the duration of the preceding fatigue periods. Internally, rest is obtained by the utilization of the simplest, softest bland diet which can be made satisfactory to the patient. At this time eggs, meat and fish are absolutely contra-indicated, as being potentially putrefactive substances. The duration of the early stage of convalescence covers usually from one week to one month.

The intermediate stage covers perhaps the next two months of convalescence. During this period the diet is gradually amplified and the patient begins to approximate more nearly normal conditions in the manner of his daily work. During this stage it is important to warn the patient that it is impossible to expect continuous recovery. The usual sequence of events is that the proportion of good days to bad increases and that the intensity of the undesirable complaints becomes less. As a rule there will be at least two or three opportunities to demonstrate to the patient the fallacy of his allowing himself full liberty of action simply on account of a sensation of well-being too early in the progress of convalescence. The invariable result of this procedure is subsequent collapse, or at least a definite setback in progress, and there is usually opportunity to prove that a single indiscretion may not be wholly recovered from for as much as one or two weeks. The word indiscretion is applied both to the expenditure of bodily and mental effort and to the excessive use of undesirable foods.

The late stage of convalescence covers from two or three months to a year or more, since if the patient has properly learned his lesson he may continue to improve in a general way over perhaps two or three years. This is a period of active experimentation on the part of the patient. Having learned his lesson it is for him to determine how nearly he can approximate a so-called normal standard of work and then to realize that every excess beyond his own limit must be paid for by a relative return of the symptoms from which he has become free. It is therefore for him to determine whether the emergency justifies the sacrifice which he knows must follow.

There are five totally distinct factors of value in treatment. These are grouped under the following headings:

1. Social.
2. Mental.
3. Dietary.
4. Orthopedic.
5. Glandular.

They are discussed at some length in another paper,<sup>12</sup> three paragraphs from which are here quoted.

"The dietary employed is based in part upon a consideration of the large amount of work by many reputable investigators, which tends to prove the ease with which the intestinal flora can be changed by a modification of diet, also upon a consideration of the fact that ileal regurgitation is an exceedingly common finding in the chronic intestinal type of invalid. Ileal regurgitation was, for instance, demonstrated in 80 per cent. of a consecutive series of fifty chronic intestinal invalids. Eggs, meat and fish, as being potentially putrefactive, are at first absolutely excluded from the dietary and the use of milk is restricted to the amount ordinarily employed in cooking. After a few weeks of complete exclusion of the above foods it is very common to find that the patient's skin is distinctly less muddy. Slowly the yellowish color of the skin is replaced by white and then by pink, a transition which is greatly appreciated by the average woman patient. During this preliminary period of marked restriction of the diet bran and the coarse vegetables are eliminated. No diet list is given, the patients being thus required to use their own brains in the working out of a suitable dietary. One advantage of this system is that the patient gradually acquires an adequate dietary for which he has the least possible dislike. If the dietary actually employed by the patient is written out and continually checked up at successive visits the results seem better from the point of view both of interest of the patient and of the physician, than if a diet slip is handed the patient at the first visit. Eggs, meat and fish are rigidly excluded from the diet for at least one month. During the latter part of this month, however, there is an increasing use of eggs as a flavoring in puddings or other cooked dishes, in which the eggs are finely divided by mixture with the various carbohy-



drates or vegetables. Meat gravies as relishes precede the use of meats as such. During the month of restricted diet, liberal use is made of two special articles of food in conjunction with the usual fruits, starches, vegetables and fats. These two articles are cream cheese (or perhaps the ordinary cheese when used as a flavoring in various cooked dishes) and gelatin. The frequent use of flavored gelatins in the form of salads or desserts is encouraged. The necessary minerals and the water and fat soluble vitamins are provided for by the use of raw fruit and green vegetables and a good grade of butter. In this connection it is surprising to discover how few people are acquainted with the virtues, both from a financial and an economic point of view, of chopped raw cabbage. This food as a salad with French dressing has been taken time and time again without the slightest discomfort or after-effects by patients who had previously stated that they could not possibly eat such a coarse vegetable.

At the end of a month or six weeks if the progress of the patient justifies it—as evidenced by decreased constipation, lessened irritability, lessened disturbance from gas, better appetite and sleep, better color of the skin, and fewer headaches—meat is put back into the dietary at first once a week. The intervals between the days on which meat is used are thereafter shortened according to circumstances. But in the chronic intestinal invalid it has been found most unusual, if meat, eggs or fish as such can be handled with comfort more frequently than two or three times a week. The intermittent use of eggs, meat and fish has another virtue in addition to its economy and its tendency to discourage the growth of undesirable intestinal flora. If the patient has only to wait over one or two days of restricted diet before being allowed a day of full diet, there seems to be much less desire for large quantities of these potentially putrefactive foods, which are handled with difficulty certainly in all patients with demonstrated ileal regurgitation.

In practice, on completion of the history, physical examination and the routine roentgen examination of the gastro-intestinal tract, of which fluoroscopic study of an opaque enema is an essential element, the social and mental factors receive first consideration in the progress of treatment. As soon as these factors are, so to speak, stabilized the diet is taken under serious consideration. In conjunction with diet frequent use is made of mineral oil, agar, yeast and atropin, and every attempt is made to take advantage of habit formation and the natural rectal reflexes. As soon as the diet has become satisfactory the application of orthopedic procedures follow, and finally comes the use of the glandular preparations when indicated. Thus by the end of the first month or so all five of these totally independent factors are being simultaneously employed in the effort to bring about as rapidly as possible an improvement in the general condition of the patient. Belts are rarely used, since

they tend to decrease the faith of the patient in his own ability to carry himself through his day's work. Only slight attention is paid to the question of weight, provided there is not a progressive loss in weight. Not infrequently one may find an apparently healthy person of almost incredible thinness. On the other hand excessive fat is no guarantee of health. Usually, however, the very thin patients will put on at least from ten to fifteen pounds in the course of a few months without apparent effort if otherwise satisfactory progress is being made."

Case,<sup>13</sup> who has devoted serious consideration to this question, has stated that if the ileocecal mechanism is once incompetent it is always incompetent. This is doubtless true in the majority of cases, but not always, as indicated by a case reported by the writer,<sup>14</sup> in which reëxamination at the end of one and two years, of a patient with previously demonstrated ileal regurgitation, proved that the regurgitation was no longer present. Kellog,<sup>15</sup> one of the few persons in this country who has taken ileocecal incompetence seriously, has even advised operation<sup>16</sup> for the restoration of the ileocecal mechanism. Without discussing the actual merits of this procedure it may be stated that in practically all cases satisfactory results in the way of treatment have been obtained by the writer by non-surgical procedure. Numerous cases have been reëxamined at various intervals after treatment. If the ileocecal mechanism is still found deficient it has at least been found to be much less so than at the original examination, and there has also been observed in every case a striking improvement in the general tone and action of the colon. One may therefore say in regard to operative treatment that it is usually unnecessary, since satisfactory results can be obtained without it and in the absence of the risks involved by operation.

VII. RESULTS OF TREATMENT. Application of the method of treatment outlined above has yielded the following results in the consecutive series of fifty chronic intestinal invalids upon which this paper is based.

No improvement . . . . .	6 per cent.
Improvement . . . . .	8 "
Improvement plus . . . . .	86 "
Total improved . . . . .	94 "

In the group of three cases constituting the 6 per cent. considered not improved is included one case with ileal regurgitation and concomitant diabetes. Treatment was practically refused for fear of upsetting the diabetic treatment. With this case excluded the percentage of cases in which no improvement in the general condition was obtained is obviously lower than 6 per cent. On the other hand the obtaining of a marked or satisfactory degree of improve-

ment in 86 per cent. of 50 cases, makes it possible to speak with some assurance concerning the prognosis, when first asked about this matter by a patient who may be in a state of mental perturbation as a consequence of frequent previous medical failures.

On the basis of the above results it is justifiable to tell the chronic intestinal invalid that he has a better than 90 per cent. prospect of improvement and a better than 80 per cent. prospect of being very much improved as a result of a few months of non-surgical treatment. This applies to the cases in which ileal regurgitation is proved. For the chronic intestinal invalid without ileal regurgitation progress should be proportionately more certain and more rapid.

VIII. SUMMARY. 1. Attention is drawn to the fact that responsible physicians refuse to become interested in a morbid condition with a history dating back to the Middle Ages.

2. The conditions associated with or resulting from ileal regurgitation do not favor optimum functioning of the gastro-intestinal tract.

3. The patient with ileal regurgitation usually suffers from an increased intensity of any nervous irritability to which he may be liable, during the continuance of untreated ileal regurgitation.

4. Immediate treatment of ileal regurgitation is by simple, bland, non-putrefying diet.

5. Adequate treatment must consider every aspect of the patient's welfare.

6. The results of treatment are indicated.

IX. CONCLUSIONS. 1. Ileal regurgitation is not a normal condition. Disregard of its existence does not promote health.

2. The existence of ileal regurgitation may be demonstrated with ease and certainty.

3. In unselected gastro-intestinal material a frequency of 20 to 30 per cent. of ileal regurgitation is to be expected. In a consecutive personal series of 50 chronic intestinal invalids the frequency of ileal regurgitation was 80 per cent.

4. Marked improvement in the general condition of 86 per cent. of this series of chronic intestinal invalids resulted from treatment directed in part toward relief from the results of the ileal regurgitation itself and directed in part toward improving the general condition of the patients.

5. With easy diagnosis assured and the possibility of obtaining satisfactory results by non-surgical treatment sufficiently demonstrated, the physician who prefers to continue to ignore the existence of ileal regurgitation may expect to have his patients suffering from ileal regurgitation take matters into their own hands if they find themselves continued in a medieval status of medical neglect with regard to progressive treatment of their malady.

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THE SIGNIFICANCE OF SMALL AMOUNTS OF SUGAR IN THE URINE.

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THE clinical interpretation placed upon glycosuria has been subject to a constantly changing point of view for a number of years past. Not satisfied with the mere finding of sugar in the urine, clinical investigators first endeavored to determine the percentage content of the sugar, later the total amount excreted in twenty-four hours and still later by bringing this twenty-four-hour excretion into relation with the carbohydrate intake, they sought to ascertain the balance between this intake and the sugar output. After a time it was observed that not only carbohydrates but also proteins play a part in the production of glycosuria in advanced cases of diabetes, an observation which indicated the need of carefully balancing the total food intake against the sugar output for days and weeks as a scientific basis for diagnosis and therapy.

During this period it was generally understood that the healthy person excretes no sugar and that sugar in the urine is pathologic,

although contributions to the literature made occasional reference to the fact that sugar may appear in the urine of healthy individuals under exceptional conditions.

It also came to be understood that different individuals show a different tolerance to the amount of carbohydrate in their food, and that if this is exceeded there results a temporary or so-called alimentary glycosuria. On the other hand, clinical experience showed that many cases of diabetes remain, so to speak, actively diabetic even though they may show no sugar in the urine, for the apparent reason that renal complications gradually raise the threshold point of sugar excretion.<sup>1</sup> Thus it came to be recognized that the degree of hyperglycemia and the sugar threshold are the determining factors of the glycosuria. The whole problem of sugar tolerance was therefore put upon a more fundamental basis. The blood sugar now came to be recognized as the most important test in diabetes.

Normally the threshold point of sugar excretion is close to 0.16 per cent. blood sugar. Under conditions of health and in the early stages of diabetes it is perfectly safe to regard the appearance of sugar in the urine as an index of the hyperglycemia. In fact, some recent observations lead us to believe that after all this may be the more sensitive method of detecting a lower carbohydrate tolerance provided we have a method sufficiently delicate to estimate the amount of sugar actually present in normal urine.

Recently, Stanley R. Benedict,<sup>2</sup> the originator of the well-known qualitative and quantitative reagents for sugar in the urine, as well as of the most satisfactory method for blood sugar estimation, has introduced a reliable procedure for determining small amounts of sugar in urine. Data obtained with the aid of this method give us a much more correct appreciation of glycosuria, or glycuressis,<sup>3</sup> as Benedict prefers to term it, than we formerly possessed, and it is with this topic that the present paper is particularly concerned.

Although we have long had accurate methods for the quantitative determination of abnormally large amounts of sugar in urine the adaptation of the same methods to the analysis of urines containing small amounts of sugar (less than 0.5 per cent.) has met with only a very moderate degree of success. Since the failure to secure accurate results with urines of low sugar content was due in large part to the interfering action of creatinine, Folin<sup>4</sup> suggested the preliminary removal of this substance by precipitation with picric

<sup>1</sup> Myers and Bailey: *Jour. Biol. Chem.*, 1915, xxiv, 147. Bailey: *Arch. Int. Med.*, 1919, xxiii, 455.

<sup>2</sup> *Jour. Biol. Chem.*, 1918, xxxiv, 195.

<sup>3</sup> Benedict, Osterberg and Neuwirth: *Jour. Biol. Chem.*, 1918, xxxiv, 258. As Benedict has pointed out, glycosuria implies a sudden point at which sugar appears in the urine. Since there is no such point the term is misleading, and Benedict has suggested the term "glycuressis" as indicating an increase of sugar but not a new appearance of sugar in the urine.

<sup>4</sup> *Jour. Biol. Chem.*, 1915, xxii, 327.

acid. With this procedure he demonstrated qualitatively the presence of sugar in normal urine. At about this time one of us<sup>5</sup> was also seeking a satisfactory way of determining the sugar content of normal urine and devised a procedure combining the advantages of Folin's preliminary picric acid precipitation and the well-known color reaction between picric acid and glucose in alkaline solution. This latter reaction had already been used in the estimation of sugar in blood and is easily adaptable to the estimation of sugar in the urine filtrates. Although later work has shown that the figures obtained with this technic are probably higher than the true sugar values, nevertheless the figures show not only the quantity of sugar present in hourly specimens of normal urine but also the effect of glucose ingestion.

Recently, however, work in this direction has been greatly stimulated by the publication of the new Benedict-Osterberg<sup>6</sup> method for the determination of sugar in normal urine. This, too, is a modification of the Lewis-Benedict method for estimating sugar in blood, but possesses a marked advantage over all previous methods in the use of a mercuric nitrate solution for the preliminary precipitation of all interfering substances—creatinine, uric acid, polyphenols and glucuronic acid. By combining the use of this new precipitant with a carefully controlled use of the original color reaction the authors have devised a method by which they can determine what they believe is very nearly the true sugar (reducing carbohydrate) of normal urine. In the experiments reported thus far they do not differentiate glucose qualitatively but simply determine the total sugar and the sugar fermentable by yeast by difference.<sup>7</sup>

In the work reported below we have made use of the Benedict-Osterberg technic essentially unchanged.<sup>8</sup> For the determination of total sugar, however, we have obtained uniformly satisfactory results by using only 10 c.c. of urine and making the subsequent filtrations through small filter papers, but without the aid of suction. In the development of the color we have employed tubes graduated to 15 and 20 c.c. instead of 12.5 and 25 c.c. as suggested by Benedict.

The general plan of our observations was to follow the hourly elimination of sugar for several consecutive hours, both in normal individuals and in those with a lowered sugar tolerance, in order to observe the effect of ingestion of food, the relation of sugar content

<sup>5</sup> Myers: *Proc. Soc. Exp. Biol. and Med.*, 1915-16, xiii, 178.

<sup>6</sup> Benedict and Osterberg: *Jour. Biol. Chem.*, 1918, xxxiv, 195.

<sup>7</sup> Benedict and Osterberg: *Studies in Carbohydrate Metabolism. I. A Preliminary Report on the Sugar Elimination in the Urine of the Normal Dog*, *Jour. Biol. Chem.*, 1918, xxxiv, 209. Benedict, Osterberg and Neuwirth: *Studies in Carbohydrate Metabolism. II. A Study of the Urinary Sugar Excretion in Two Normal Men*, *Ibid.*, 1918, xxxiv, 217. For a general discussion of the sugar of normal urine, reference may be made to these papers.

<sup>8</sup> Professor Benedict has recently informed us of a greatly simplified technic which he has developed for this estimation.

to volume and the relative value of the ordinary qualitative test (Benedict's) compared with the new quantitative one. In every case the experiment was started at 10 A.M., since at that hour the assimilation of breakfast was practically complete and the process of carbohydrate metabolism might reasonably be assumed to be at its lowest day level.

TABLE I.—CASES WITH NORMAL CARBOHYDRATE TOLERANCE.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
			CASE	R. T.				
10 to 11 . .	110	—	0.025	28	43	14	57	14
11 to 12 . .	475	—	0.004	19	26	5	74	14
12 to 1 . .	290	—	0.011	32	47	15	53	17
1 to 2 . .	255	—	0.013	33	55	18	45	15
2 to 3 . .	170	—	0.044	75	39	29	61	46
3 to 4 . .	140	—	0.040	56	43	24	57	32
4 to 5 . .	330	—	0.010	36	53	19	47	17
	1770			279		124		155
			CASE	W.				
10 to 11 . .	25	±	0.099	26	46	12	54	14
11 to 12 . .	24	±	0.103	26	65	17	35	9
12 to 1 . .	30	+	0.152	46	76	35	24	11
1 to 2 . .	42	+	0.144	61	82	50	18	11
2 to 3 . .	44	±	0.064	28	61	17	39	11
3 to 4 . .	27	—	0.070	19	63	12	37	7
4 to 5 . .	94	—	0.039	37	59	22	41	15
	286			243		165		78

Case R. T. Dinner at 11.30, consisting of cream soup, mashed potato, lima beans, corn starch, bread and butter, milk

Case W. Dinner at 11.30, consisting of baked potato, cream soup, fish, corn starch, milk.

Table I shows hourly sugar excretions of two patients with normal sugar tolerance. Both of these cases show clearly the gradual increase in the actual amount of sugar excreted after the ingestion of food. Moreover the figures for Case W show the importance of determining the actual number of milligrams of sugar rather than the percentage of sugar excretion. Although the actual quantity of sugar excreted was slightly less than that excreted by Case R. T., yet owing to the relatively small volumes several of the specimens from Case W. gave definitely positive qualitative reactions. Despite this fact, however, the rate of sugar excretion is perfectly normal in both cases, as observation of a large number of individuals would indicate that a normal adult excretes about 1 gm. of reducing sugar in twenty-four hours.

TABLE II.—CASE (L. F.), WITH SLIGHTLY LOWERED CARBOHYDRATE TOLERANCE.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
10 to 11 . .	85	—	0.044	37	49	18	51	19
11 to 12 . .	40	±	0.079	32	19	6	81	26
12 to 1 . .	51	++	0.928	473	65	308	35	165
1 to 2 . .	65	++	0.610	397	78	309	22	88
2 to 3 . .	47	±	0.067	32	59	19	41	13
3 to 4 . .	95	±	0.047	45	44	20	56	25
4 to 5 . .	29	±	0.060	18	44	10	56	8
	412			1034		690		344

Dinner at 11.30, consisting of 200 c.c. of broth, potato, chicken, two slices of bread, rice pudding, 180 c.c. of milk.

TABLE III.—CARBOHYDRATE TOLERANCE OF DIABETIC PATIENT (A. MC W.), MORNING URINE REPORTED "SUGAR-FREE" FOR TWELVE DAYS FOLLOWING TREATMENT.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable Sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
10 to 11 . .	140	—	TEST I.	21	48	10	52	11
11 to 12 . .	340	—	0.015	34	58	23	32	11
12 to 1 . .	45	—	0.010	21	21	5	79	16
1 to 2 . .	22	—	0.046	18	11	2	89	16
2 to 3 . .	92	++	0.085	754	96	720	4	34
3 to 4 . .	60	+	0.820	89	74	66	26	23
4 to 5 . .	360	—	0.148	126	78	98	22	28
	1059			1063		924		139
10 to 11 . .	33	—	TEST II.	24	46	11	54	13
11 to 12 . .	265	—	0.072	22	41	9	59	13
12 to 1 . .	145	+	0.006	420	92	387	8	33
1 to 2 . .	150	+++	0.290	4,370	99	4,332	1	38
2 to 3 . .	145	+++	2.920	6,453	99	6,414	1	39
3 to 4 . .	360	++	4.450	3,528	98	3,449	2	70
4 to 5 . .	535	+	0.980	1,712	95	1,627	5	85
	1633			16,520		16,229		300

Test I. Dinner at 12.30, consisting of 240 c.c. vegetable soup, broiler, stuffed potato, bread and butter, spinach, ice-cream, lady-finger, tea.

Test II. Dinner at 11.30, consisting of baked potato, two slices of bread and butter, cup of custard, 180 c.c. of milk.

That slight impairment of sugar tolerance may easily pass unnoticed in routine urine examinations is demonstrated by Case L. F. Routine specimens taken before breakfast (morning urines) were



consistently reported as negative, but one hour after the ingestion of luncheon the actual sugar excretion rose from 32 mgm. per hour to 473 mgm. per hour. Hourly specimens from 12 until 2. o'clock gave a marked positive reaction, and in a period of two hours there was excreted a total of 870 mgm. of sugar, a quantity almost equal to a normal twenty-four hour output.

These figures serve to call attention again to the well-known but often neglected fact that in diabetes the customary qualitative routine examination of urine is frequently of very little value. These examinations are usually made on a specimen collected before breakfast, perhaps twelve hours after the last meal has been eaten. Under such conditions the urine may show no effect from the last ingestion of food, and the test may give very misleading results.

Such a case is reported in Table III. This patient had been reported "sugar-free" every day for twelve consecutive days. The results tabulated here, however, show that in a single hour after a low carbohydrate luncheon the patient excreted 754 mgm. of sugar, while three hours after a moderate carbohydrate intake the excretion was 6.5 gm.

TABLE IV.—OBSERVATIONS ON F. T., A MILD DIABETIC OF LONG STANDING.

Hour.	Volume, c.c.	Benedict's qualitative test.	Total sugar.		Fermentable sugar.		Unfermentable sugar.	
			Per cent.	Mg.	Per cent.	Mg.	Per cent.	Mg.
10 to 11 . .	107	+	0.245	262	83	218	17	44
11 to 12 . .	62	+++	1.660	1030	98	1011	2	10
12 to 1 . .	59	+	0.300	127	87	110	13	17
1 to 2 . .	52	+	0.072	37	59	22	41	15
2 to 3 . .	47	—	0.050	24	33	8	67	16
3 to 5 . .	150	—	0.031	46	50	23	50	23
5 to 6 . .	50	—	0.060	30	43	13	57	17
	527			1556		1405		151

Breakfast at 10 o'clock, containing about 50 grams carbohydrate.

From a clinical point of view the data presented in Table IV are perhaps the most interesting of any we have obtained. F. T. has had diabetes for several years, but on a restricted diet has been "sugar-free." Recently, however, while making the Benedict qualitative test on his own urine he obtained a positive reaction. Similar tests for several successive days gave negative results, but in spite of this he came to the laboratory for blood and urine examinations. At our suggestion he made no change in diet but ate his regular 50 gm. carbohydrate breakfast at 10 o'clock, collecting specimens hourly thereafter. It is interesting to note that during the second hour after breakfast the percentage of sugar was 1.6,

but during the fourth hour it dropped to 0.07 per cent., and after the fourth hour the qualitative test gave a negative result. Obviously in such cases as F. T. the ordinary qualitative test on an occasional specimen may be very misleading.

Further presentation of figures seems unnecessary in order to emphasize the practical value of the work outlined above. The use of the method demonstrates more clearly than ever before the error of the idea that glycosuria is a sudden phenomenon. The elimination of sugar through the urine is a continuous process, quite independent of the volume of the urine, but showing a definite increase after the ingestion of food. This increase in absolute quantity of sugar in the urine, or glycuressis, as Benedict calls it, follows in a greater or less degree the mere process of digestion, although the actual food consumed may contain no sugar whatever.

Along with this deeper conception of sugar excretion the new method affords the clinician valuable aid in the attempt to diagnose and treat cases in which as yet the sugar tolerance is only slightly lowered. Because of the low concentration of the sugar in the urine the old qualitative tests with copper solutions may frequently give misleading results in cases of slightly lowered sugar tolerance, but the use of the new technic on a twenty-four hour specimen makes an accurate determination of the exact sugar output a relatively simple matter. An occasional determination of this sort could scarcely fail to be of far greater value in the treatment of the case than the customary qualitative analysis.

**Conclusion.** It would appear from qualitative sugar observations on hourly specimens of urine, a few of which are given in the present paper, that the results obtained with the usual qualitative tests made upon specimens of urine taken at random, or even in the morning before breakfast, are quite misleading as regards the carbohydrate tolerance of the patient.

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#### PATHOGENESIS OF ACUTE LEUKEMIA: REPORT OF A CASE OF ACUTE MYELOBLASTIC LEUKEMIA, WITH THE ASSOCIA- TION OR COMPLICATION OF VINCENT'S ANGINA.

BY MAURICE PACKARD, M.D.,

AND

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PATIENT, R. M., nativity, Poland; occupation, operator; aged twenty-six years. Admitted to Gouverneur Hospital, March 7, 1920. Died March 12, 1920.

*Family History.* Ignorant of conditions of relatives in Poland. Knows of nothing unusual in family.

*Previous History.* Patient is married. In addition to her household duties she worked daily as an operator in a clothing factory. Usual diseases of childhood. Denies venereal infection. Her health has always been good. She has been married seven months. No pregnancies. Menses regular. No previous attacks.

*Present History.* Patient was in excellent health until two weeks prior to admission. Her illness dates from a day on which she washed her hair, and before it was dry she went into the street to do her marketing. Shortly after her return there developed a severe headache, and her ears, neck and shoulders pained her. These complaints continued, and shortly afterward she noticed a sore on the mucous membrane of the right cheek. This rapidly spread until it involved the gums of the upper right alveolar ridge and the mucous membrane of the hard palate. Coincident with the extension of the lesion in the mouth there developed a swelling under the jaw, first on the right side and then on the left side. As this swelling increased in size it became difficult for her to swallow or to speak. She cannot state whether she had a fever. She was refused treatment for her mouth lesion at one of the hospitals of the city. A neighbor cared for her, with various mouth washes, until the odor from the sore in the mouth became foul. Patient then sought admission to the hospital.

*General Appearance.* Recumbent adult; female; pallor marked; face and neck swollen; some difficulty in breathing.

*Eyes:* Pupils equal and regular, react to light and accommodation. *Mouth:* Patient breathes through the open mouth; teeth in poor condition; gums slightly congested; no bleeding from gums; there is a foul-smelling, black, membranous exudate, with a well-defined margin on the roof of the mouth extending slightly beyond the midline on the left and continuous with a like lesion on the gums of the right upper alveolar ridge; there are several lesions of similar appearance on the right cheek, the left cheek and the left upper alveolar ridge on its external surface.

*Tongue:* Slightly swollen; no leukoplakia or other lesions.

*Throat:* Swelling of right peritonsillar tissue; right tonsil prominent but is free of exudate; pain and fluctuant sensation elicited pressure over the right antitonsillar pillar; there is inability to separate the jaws more than three-quarters of an inch.

*Neck:* Painful, massive and conglomerated swelling of submaxillary lymph nodes on both sides, the right more prominent than the left.

*Heart:* No enlargement; no thrill; no abnormal impulse; rate increased; no murmurs; sounds feeble.

*Arteries:* Negative.

*Pulse:* Tension fair, quality poor.

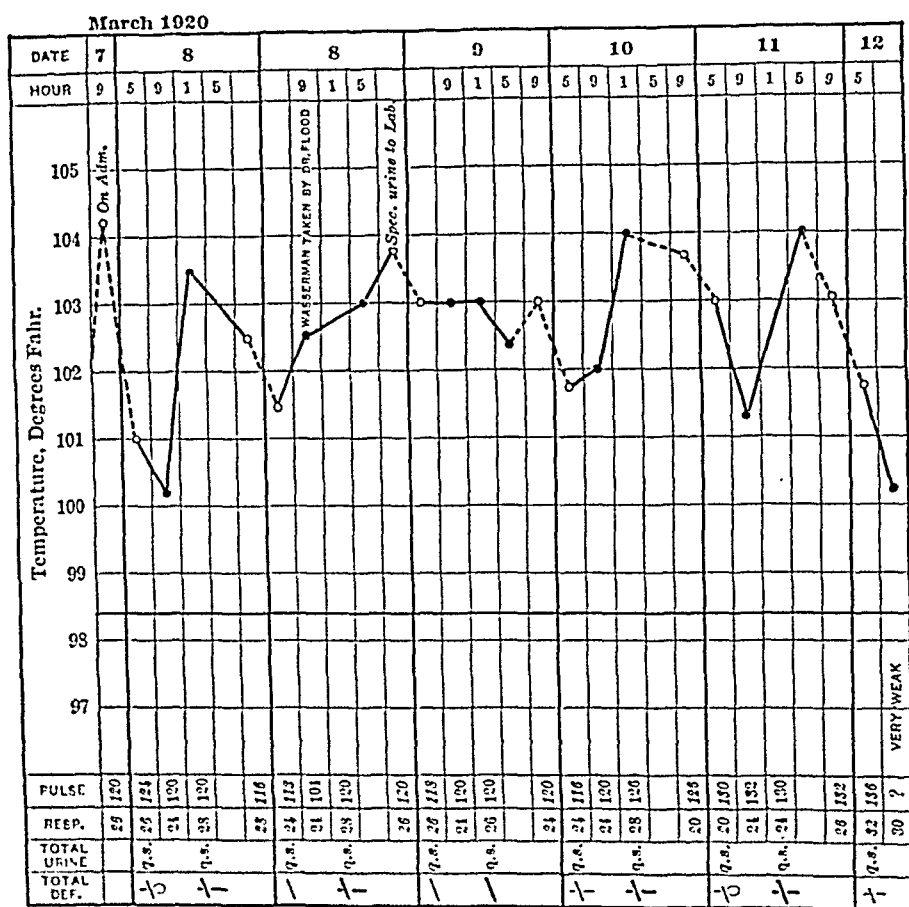
Lungs: Slight dulness; cogwheel breathing at right apex posteriorly; clear and resonant elsewhere.

Abdomen: Scaphoid; no rigidity; no masses.

Liver: Not enlarged.

Spleen: No enlargement made out on percussion and palpation.

Kidneys: Not felt.



Skin: Pronounced eczema of scalp; numerous small hemorrhages along hair line of forehead.

Skeletal Structures: Negative.

Lymphatic System: Discrete and shotty enlargement of post-cervical, epitrochlear and inguinal lymph nodes.

Reflexes: Present and active.

#### CLINICAL PATHOLOGY.

March 8, 1920. *Urine.* Transparency, cloudy.

Color, amber.

Reaction, alkaline.

Albumin, heavy cloud. Glucose, 0.

Stained smear of mouth lesions shows many spirilla and fusiform bacilli.

Acetone, 0.

Casts, many.

Leukocytes and pus, few white cells.

March 8. Culture of mouth lesions negative for *Bacillus diphtheria*.

#### BLOOD EXAMINATION.

March 9, 1920. Leukocytes, 190,000.

Number of cells counted, 300.

Polynuclears, 290.

Transitionals, 15. March 10, Wassermann negative.

Lymphocytes, 26.

Myelocytes, 18.

Myeloblasts, 10.

Hb. per cent., 60. Instrument, Sahli.

Erythrocytes, 2,950,000.

Normoblasts, 2.

March 12. Blood smears, reported by Dr. L. Unger, showed nucleated red blood cells together with anisocytosis and poikilocytosis. There is a tremendous increase in the number of white blood cells, which are chiefly myeloblasts. One per cent. myelogenes, a forerunner of the myeloblast is present. A large percentage of the myeloblasts show evidence of considerable degeneration. In the body of some myeloblasts an erythrocyte is seen. This ingestion of erythrocytes is evidence of the terminal stage of the disease. A small percentage of myelocytes are present.

The smear stained for the oxidase reaction is positive. The differential count of the white blood cells on March 10, 1920, date of death, were as follows:

Polymorphonuclears: Neutrophiles, 3 per cent.; eosinophiles, 0 per cent.; basophiles, 0 per cent.

Small lymphocytes, 3 per cent.

Large lymphocytes, 0 per cent.

Myeloblasts, 90 per cent.

Myelocytes, 3 per cent.

Myelogenes, 1 per cent.

Anisocytosis, moderate.

Poikilocytophilia, moderate.

Polychromatophilia, none.

#### REPORT OF SOCIAL SERVICE INVESTIGATION.

Home of patient fairly clean; no stove in rooms; patient did cooking on neighbor's stove; patient and husband worked during day; neighbors state that their food was apparently adequate and of good quality.

March 8. Patient examined by nose and throat consultant. Suspicion of scorbutus. Findings: marked necrosis of the lower jaw. Severe tenderness on pressure over the right canine fossa.

March 9. Patient breathing easier; less apathy; no improvement in mouth lesions.

March 11. Patient much weaker; takes no food; marked inspiratory dyspnea.

*Diagnosis:* Acute myeloblastic leukemia.

*Treatment:* Consisted of arsphenamin locally to mouth and intravenously.

When one has the opportunity of studying a case of acute leukemia he must necessarily be impressed with its peculiarly infectious-like type of onset and course. Yet strange as it may seem to him the conclusion that acute leukemia is an infection has been held as untenable by a number of competent investigators.

Since the day of Newman, who in 1870 showed the marrow lesions in leukemia, the contention of Lowitz, who held that leukemia was a disease of the blood itself, has been discarded. Although the bone-marrow, and especially the lymphoid tissue of true bone-marrow, has been accepted as the principal affected tissue, yet the exciting cause is still surrounded with a great deal of uncertainty. The widespread occurrence of leukemia in all animals, according to Warthin, speaks against infection and corresponds to a neoplastic growth. One cannot help wonder if it is a tumefaction or a sarcomatous condition (Banti), why the condition does not progress in a steady advance and why the blood does not correspond to the condition. The peculiar remissions which occur so frequently do not correspond to the usual course of a tumor. The spontaneous *bona fide* cases of cure, which occur in myeloblastic leukemia, again seem to us to oppose the theory of tumefaction. A white blood count under 25,000, notwithstanding the number of myelogenes, myeloblasts or other cells, augurs well for the patient, and a cure in such instances can at least be hoped for.

Although no specific organism has been satisfactorily demonstrated as the etiologic agent in leukemia, still there has been quite an accumulation of corroborative evidence that the basic factor in its production must be an infection.

Ellermann and his co-workers in Copenhagen claimed to have produced either myeloid or lymphatic leukemia or an anemia without leukemia in chickens by means of a filtrable virus. Although his work has been impressive, still others and very competent workers were unable, with practically the same technic to produce his results. It is well to recall here that chicken leukemia is not exactly like human leukemia for chickens do not have lymph nodes, with the exception of the cervical region, and this corresponds histologically to the thymus in the human. Clinically therefore we would not have any lymphatic swellings, an important sign in true leukemia.

The literature abounds with other claims of certain bacteria producing the lesion. Cabot presents an interesting contribution but not conclusive by any means, because of the dangers of coincidence, of a nurse who became a victim of leukemia while nursing a leukemic patient. Again, there have been the stories of the epidemic of leukemia, one in the valley of Enz in 1905 and another in Toulouse in 1912. The stories of these epidemics can hardly stand the light of day, as the record, for instance in Toulouse, of 18 cases of all classes of leukemia in twenty-two months wherein previously leukemia was very rare in this region, counts very little as a bullet-proof conclusion.

In rebuttal of their evidence and thinking from an infectious standpoint, it is rather hard to reconcile the incontrovertible proofs of cases wherein a number of leukemic mothers have given birth to healthy children. There are at least a dozen of such instances in the literature.

There is no question that the clinical symptoms, such as the temperature, swollen spleen, hemorrhagic condition of the mouth, tonsils and intestinal symptoms, would make one favor an infectious origin, but in leukemia we have so many secondary invaders that it is difficult to recognize just what symptoms are really leukemic and just what are due to a secondary invader.

Dorothy Reed, in her opinion, has summed up the evidence very tersely when she says that it is due to some chemotaxis in some part of the body, with a peculiar predilection for myeloid tissue.

Packard and Ottenberg have described a peculiar leukotoxic state in the lymphatic variety.

Bearing upon our own work it is well to recognize that in lymphatic leukemia about one-tenth of the leukocytes are absolutely in a degenerative state, and in one case reported by Emerson the leukocytes would not stain at all.

It is interesting to note that Rotky, in 1900, stated that the blood in leukemia has no agglutinating power to bacteria and that, to my mind, not only explains the apparent incapacity for production of antibodies, but also explains the lack of resistant power in leukemic patients to otherwise harmless infections. Again, it gives us a practical clue to the number of bacteria which have been brought forward as the specific etiologic agent.

Sondern, in a personal communication (although he feels that he is not quite justified to report this) feels that in a number of instances Vincent's organisms might have been the exciting factor. He has found Vincent spirillum and the fusiform bacillus in twenty-two cases, and in two cases he is convinced that it preceded the leukemia and was the important agent in causing the condition. In two other cases he has had a lymphemic state with over 95 per cent. of lymphocytes. In one case of a child, nine years elapsed before the blood returned to normal and in another case an interval of five years before the blood again became normal.

Again and again I am seeing severe lymphemias with symptoms of leukemia, which after a time proceed to get well so that we necessarily hesitate now and then to give a hopeless prognosis as one ought to if he were absolutely certain that he was dealing with leukemia.

In the army Vincent's angina was considered a very harmless infection. It was found most often in trench mouths. But in our experiences when it is associated with leukemia it is a most potent factor in producing an early death.

To summarize then the complete story of the etiology, leukemia still has an unfinished chapter. The evidence in favor of an infectious theory is rather preponderating, but still far from conclusive. The best we can say as to its causation is to requote Dorothy Reed, when she concluded that it is due to some chemotaxis, with a special predilection for the bone-marrow.

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#### THE CONTENTS OF THE STOMACH: ITS STUDY AND INTERPRETATION.

By ELBRIDGE J. BEST, M.D.,

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By glancing through the literature one sees the wide acceptance of the small tube as a means of removing the stomach contents by the fractional method, thus enabling one to study the activity of the stomach continuously over a period of hours. Although used by Europeans as early as 1912,<sup>1</sup> it was first brought to the attention of



the American profession by Rehfuß<sup>2</sup> in 1914, who later enlarged upon the benefits to be gained by the "fractional" study of the stomach contents. Our knowledge of the stomach activity as well as our ability to diagnose pathologic conditions has increased thereby manifold. Much constructive work has been done by Crohn<sup>3</sup> and others. Yet the impression one gets from the literature is that each worker has many little points in technic and methods of procedure that differ from the others and which are never clearly explained in print. For that reason it seems wise to state our method of studying the stomach contents in the clinic in an attempt to keep this phase of stomach examination more uniform and possibly promote wider discussion and use.

The procedure is as follows: The evening before the test the patient is instructed to eat two or three prunes or raisins before retiring. He appears at the clinic at 8 A.M., having taken nothing since the night before. A Rehfuß<sup>2</sup> tube is passed and the contents of the fasting stomach completely removed, measured and examined. The technic of introducing this tube was described in a former paper,<sup>4</sup> from which I quote: "This is done by having the patient open his mouth and say 'Ah.' " The metal tip is dropped behind the tongue and the patient swallows. To prevent gagging and retching the patient takes deep breaths. When this is done the tube can be passed to the 50 cm. mark with hardly an unpleasant sensation to the patient. When down the tube is kept to one side of the throat and causes very little annoyance. During this period the patient can talk, read or devote his attention toward any minor employment to pass the time. Saliva is frequently abundant. The patient is instructed to spit this out, not to swallow it." The tube is removed and the patient is given an Ewald test breakfast. (An oatmeal gruel is used by Crohn, given with the tube still in place. Others, I have learned, feed the gruel through the tube. However, if one wishes to reach as nearly the normal secretion as possible, it seems logical to avoid having a tube interfering with mastication or depriving the patient of the stimuli of taste and chewing. It seems a small but very essential point to bear in mind the physiology of the digestive secretions as is demonstrated by the works of Pawlow<sup>5</sup> and Boldyreff.<sup>6</sup> Also I have determined the HCl deficiency of the oatmeal gruel and find it quite the same as that of bread and water. I therefore feel the advantage lies with the simple bread and water meal which demands definite mastication.)

One-half hour following the beginning of the meal the tube is again introduced and 3 to 5 c.c. of contents removed. This is repeated every fifteen minutes until the two-hour period. At that time all the contents is removed, measured and tested. Each time the sample is withdrawn I insist on a little air being blown back, both before and after, to assure the purity of each specimen.

Such a procedure gives us abundant information. Motility, re-

tention, hypersecretion, presence or absence of normal and abnormal acids and ferments, bleeding, presence of pus or exfoliating gastric mucosa, abnormal albumin and malignant cells can be determined.

In the contents of the fasting stomach the presence of prune or raisin skins speaks for retention. Normal stomachs twelve hours after a meal contain less than 100 c.c. of contents. Over this amount is found in retention and hypersecretion cases. The concentration of acid varies greatly from no free HCl and low total to very high acid which may be almost pure HCl. The presence of bile in these specimens is quite normal. One of the most important items in the study of the fasting contents is that of the microscopic elements. Here we look for pus and blood cells, the character of the gastric epithelial cells and the presence of cells with mitotic figures representing malignancy, which incidently are very rarely seen. The cells are studied in the fresh and stained preparations. Yeasts and flagellates may be found or Boas-Oppler bacilli may be seen when present. For the more complete study of the microscopic elements, as described by Leoper and Binet,<sup>7</sup> while the tube is in the stomach one can introduce 30 c.c. of normal salt solution and immediately withdraw it, centrifuge the fluid and study the sediment in the fresh and stained condition. When malignancy may be suspected, modifications of the Wolff-Junghaus and allied tests can be carried out for the presence of abnormal albumin and proteolytic ferments.

The removal of only a few cubic centimeters of stomach contents, during the two-hour observation, is to prevent one from removing too large a quantity each time and thus interfere with the stimulation of the meal on the stomach secretion. Also by using 1 c.c. of content and titrating with  $\frac{1}{100}$  normal sodium hydrate the buret reading gives the same figure as the use of 10 c.c. of content and one-tenth normal sodium hydrate.

For studying the presence of the ferments in the patients who show no free HCl during the two-hour period the one-hour specimen is selected, filtered and incubated with coagulated egg-albumen as is ordinarily carried out.<sup>8</sup>

After having determined, by titration, the amount of tenth normal hydrochloric acid and total acid in 100 c.c. of the fasting contents and in the fifteen-minute samples over the two-hour digesting period to properly study the findings obtained it is necessary to plot curves, using the acid values as ordinate and the time as abscissa, which portray the actual progress of the acid concentration. In other words, we graphically visualize the ever-changing chemical condition as it exists in the stomach during that period of digestion examined. The advantage of these curves in its superiority over the older "one sample test" that a few clinics still persist in using, is comparable to the advantage of the moving picture over a single snapshot.

These curves may or may not be of great value, depending upon how they are interpreted. Many clinicians, having expected to obtain direct conclusions from the actual acid values, have become discouraged with the fractional method and labeled it as quite

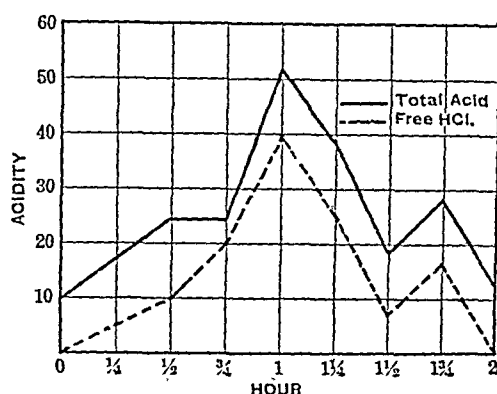


FIG. 1.—Type I, "normal," fasting content 25 c.c.; apex in one hour; one and a half-hour drop, with recovery in one and three-quarter hours seen in duodenal regurgitation.

unessential. The actual acid values mean very little. The shape of the curve means more. There are a few valuable points to look for in studying these curves: (1) Note the acidity of the fasting contents; (2) the apex of the curve; (3) the position of the curve in two hours; (4) the position of the HCl curve compared to the total

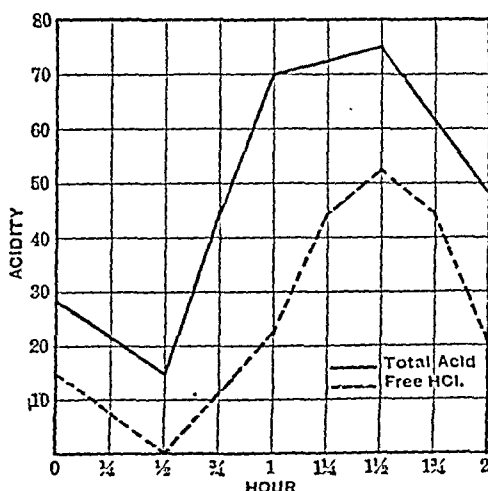


FIG. 2.—Type I, fasting content 50 c.c.; a slight variation between free and total acid curves but the shape is very similar; apex in one and a half hours.

acid curve, that is, whether it follows the total curve regularly or takes an independent and very irregular course.

There are five more or less general and distinct types of curves in which any fractional result will fall. By keeping these five types

in mind and placing the curves received in their proper group a definite knowledge of the secretory and motor activity of the stomach is obtained which becomes a positive item to aid in diagnosing the condition at hand. Type 1 (Figs. 1 and 2) begins with a moderate fasting acidity and rises to the apex in from one to one and a half hours and a steady decline. The apex may be 60 for total acid or 90. The free HCl curve follows total regularly and about twenty points below. This is considered the normal type.

There may be breaks in the smooth continuity of the curve with large sudden drops in acidity, free and total acid acting parallel. Bile may be present with these drops. Such defects in the regular outline are due to a reflux of duodenal contents into the stomach

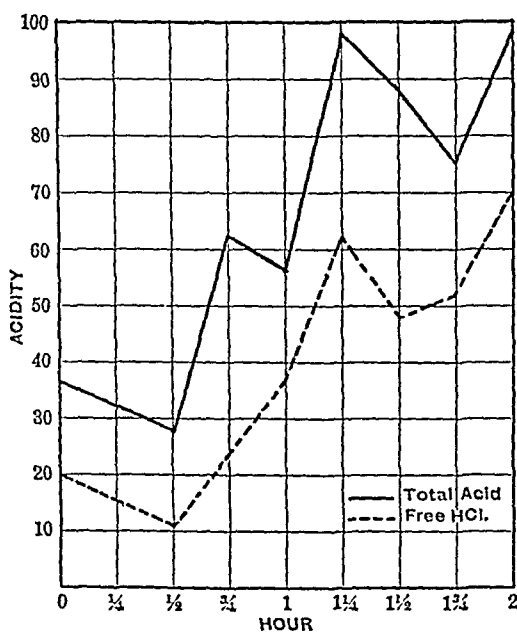


FIG. 3.—Type II, "ascending;" fasting content 50 c.c.; curves slight and irregular: but respond similarly; high point in two hours; mucus +; gastric cells +; diagnosis: duodenal ulcer, with recent hemorrhage.

and are quite a normal event, as demonstrated by Boldyreff.<sup>9</sup> If blood is discovered with such duodenal regurgitation it is the one definite evidence of pathology in the duodenum (Rehfuss<sup>10</sup>).

The second type of curve (Figs. 3 and 4) frequently has a high fasting acidity, a quick drop occurring early after the test-meal and a steady rise to the two-hour period. This is an ascending type of curve frequently showing the HCl steadily approaching the total acid curve until at the two-hour period the stomach content may be almost pure HCl and of a value near 100. This type is found in cases of gastric ulcer of not too long standing, frequently in duodenal ulcers, in recent gall-bladder infections and sometimes in subacute or chronic appendicitis. One cannot say, upon looking at a curve

of this type: "Here is a case of duodenal ulcer," but it does represent the existence of a definite abnormal condition, namely, a marked

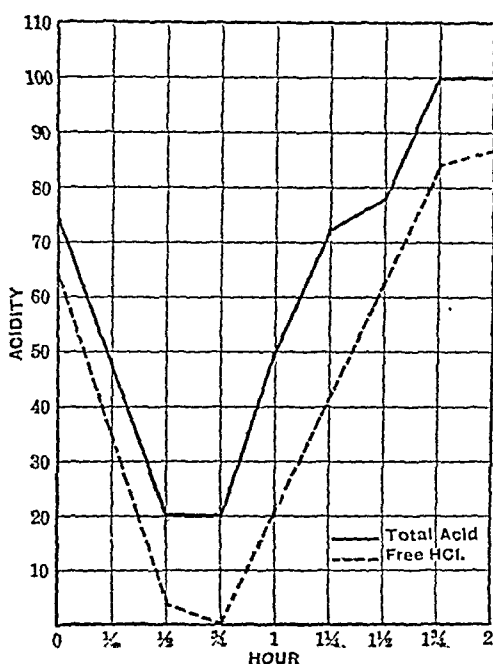


FIG. 4.—Type II, fasting content 50 c.c.; few gastric cells and leukocytes; high fasting, acid; sudden drop with meal and steady, rapid rise to apex in two hours; diagnosis: cholecystitis.

hyperactivity of the gastric secretory apparatus (McWhorter<sup>11</sup>). This hyperactivity usually extends on to the next meal. Sometimes the apex is reached in or before one hour and from that point on the curve becomes almost a horizontal line, with occasionally the appearance of a sudden drop and quick recovery to the former level.

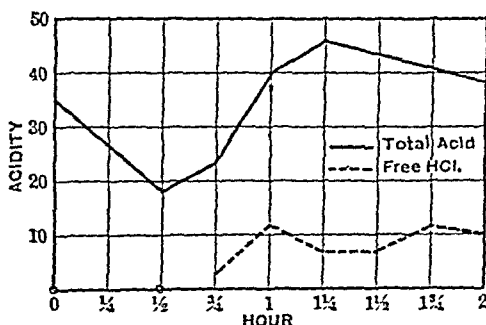


FIG. 5.—Type III, "irregular," fasting content 40 c.c.; mucoid; leukocytes +; free HCl, early absence, later low; irregular compared with total curve; total fairly normal shape; diagnosis: subacute gastritis.

The third type (Fig. 5) shows a total acid curve of possibly normal or low value, taking a fairly normal course, but with the HCl curve

very irregular and not in the least symmetrical with the total curve. The difference between the HCl and total acid values is usually over 20. Such a curve is found in cases of subacute gastritis of not too long duration or in conditions that tend to depress gastric secretion, such as chronic infective processes located at distant points, as for instance the mouth, gall-bladder and appendix. We are dealing here with a depressing influence on the secretory mechanism, possibly in some cases a direct damage to the gastric cells. We are helped, in the microscopic examination of the fasting contents, by the presence of pus, the mouth being above suspicion, or eosin-staining gastric cells, which reveal an inflamed condition of the gastric mucosa. We find cases of marked gingivitis when purulent material is expressed from between the red, swollen gums and the teeth and a curve of type three, the fasting contents showing many pus cells and squamous epithelial cells. It is reasonable to suppose there may be some local inflammatory condition of the gastric mucosa, but, without the presence of increased numbers of gastric cells, the conclusion is that the mouth infection is primary. In such cases a visit to the dentist for scaling and polishing the teeth will result in a large percentage of cures.

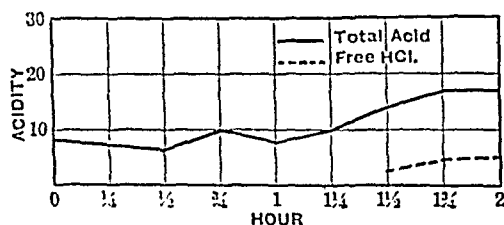


Fig. 6.—Type IV, fasting content 50 c.c.; leukocytes ++; epithelial cells +; no free HCl until late; total curve low; diagnosis: chronic gastritis and esophagitis.

The fourth type (Fig. 6) is really a progression of the third type. Here the total acid is moderately low, with a very low irregular HCl, reaching zero in one or more intervals during the two-hour period or only appearing in one or two samples. Such a curve is found in a chronic gastric inflammation of long standing, in focal infection with systemic reaction, including tuberculosis and lues and in cases of malignancy. With the last-named condition one is helped at times by finding, in the microscopic elements, cells containing mitotic figures.

The fifth type (Fig. 7) is a curve showing the total acid as having a value of about 10, holding mostly to a straight line. No HCl is discovered at any time. All of the samples look like a mixture of bread and water, with possibly the addition of considerable mucus. The ferments are entirely absent. With this curve we have the typical findings in achylia, which is not a disease but purely a manifestation of a deeper seated process. Achylia has been con-

sidered more in detail in a recent paper.<sup>12</sup> It is rather rare to find this curve in gastric malignancy but is seen no less rarely in malignancy elsewhere.

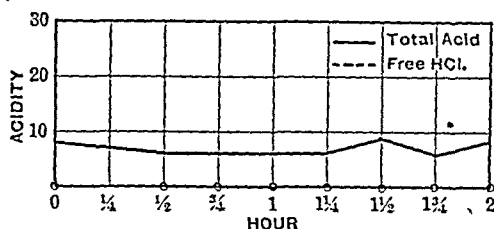


FIG. 7.—Type V, fasting content, 20 c.c.; mucus +; square epithelial cells ++; leukocytes ++; ferments absent; no free HCl; total curve a straight line under 10. This was a case of badly infected mouth and pulmonary tuberculosis.

There is one other form of curve (Fig. 8) occasionally seen in which the total acid is very low and no free HCl is found during the first hour, while the second hour result is definitely normal or similar to type 2. In this instance we are dealing with a psychic secretion (Rehfuss) during the first hour, showing inhibitory effect of nervousness, caused by the first introduction of the stomach tube, whereas in the second hour the chemical or normal secretion appears, uninfluenced by external factors. Such a curve should be repeated, at

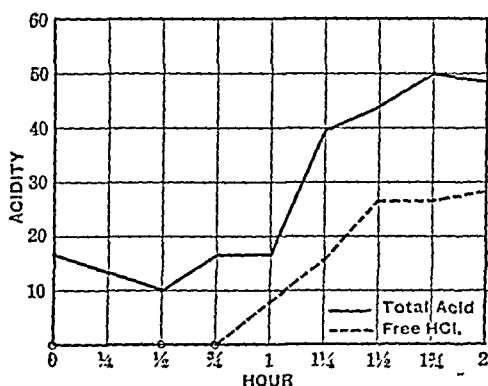


FIG. 8.—“Psychic curve,” no free HCl and low total first half of period, then rapid recovery to fairly high values. Patient thin and nervous. Result of second test similar to Fig. 1.

which time one receives a normal curve complete for the two-hour period.

Should a curve look unusual on the first day it is very advisable to repeat the examination once or twice. A steady type of curve will then be obtained which gives the secretory picture for that patient.

In many instances it has been a great help in realizing just how the free HCl curve varies in its progress from the total acid curve, to plot, in a different color, a curve for the difference between the

free and total acids. Normally, such a curve should be a straight line. Marked irregularity and unusual distance from 20 spells disturbance in HCl secretion. I have not been able to determine anything more specific in its interpretation.

Regarding the amount of secretion recoverable from the stomach two hours after the meal was begun, insufficient number of normal cases have been examined to draw conclusions. It would appear that over 100 c.c. of content definitely indicates a delay in emptying or an excess of secretion. This two-hour content usually contains but a small amount of starch, indicating most of the meal has passed the pylorus. The evidence of delay found in this last specimen, including the presence of over 100 c.c. of fluid, has been found to parallel the six-hour retention seen in the roentgen-ray examination.

**Summary.** A method is outlined for the fractional stomach examination which makes it possible to complete all the tried tests of gastric study in two hours and gives connected pictures of the secretion during this period. The procedure is simple and can be carried out by any practitioner with the aid of his nurse. The gastric curves are placed in five groups, no stress being laid on the actual acid figures, but emphasis is placed upon the position of the apex and the two-hour level of the curve, the difference between the free and total acid curves and the behavior of the free HCl curve. By repeating an examination a more stable, reliable curve is obtained. By carefully following out the above procedure it is possible to become more intimately acquainted with the detail of gastric activity, thus making it possible to carry out treatment by diet and medication in a more intelligent manner as well as making diagnoses of gastric complaints more accurate.

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## REVIEWS

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DISEASES OF THE NERVOUS SYSTEM. A Text-book of Neurology and Psychiatry. By SMITH ELY JELLIFFE, M.D., PH.D. and WILLIAM A. WHITE, M.D. Third edition. Pp. 988; 470 engravings and 12 plates. Lea & Febiger. Philadelphia.

THE third edition of the work of Dr. Smith Ely Jelliffe, of New York, and Dr. William White, of Washington, D. C., is constructed essentially on the same lines as the former two editions. The book is divided into three parts:

Part I deals with what the authors call the "Physico-chemical Systems," essentially vegetative and visceral neurology and the endocrinopathies. The recent advances made by study and research into the realms of the hormonopoietic system and vegetative neurology are incorporated into this chapter, and add much to its value. In it the authors endeavor to demonstrate more clearly the intimate relationship existing between the so-called ductless glands and the physiologic and pathologic processes in all the systems of the body, whether they be nervous, alimentary or bloodvessel. Many excellent illustrations and diagrams help to clarify this rather obscure subject for the student reader.

Part II is devoted to the "Sensorimotor Systems," being mainly organic neurology. The various observations on living pathology which the great war afforded are judiciously used to augment this chapter. Peripheral nerve injuries and gunshot wounds of the brain and spinal cord are illustrated by many photographs and diagrams.

Part III deals with the "Psychical" or "Symbolic" systems. The principal additions to this part are the articles on the War-neuroses and so-called "Shell-shock." An endeavor is made to show the relationship existing between the neuroses and the psychoses and to demonstrate the mechanism involved in the causation and growth of these disorders. Psychoanalysis, discussed in the opening chapter, is prominent throughout all of part three, and in the treatment of most of the volume the Freudian teachings can be discerned.

Altogether the third edition is much wider in its scope than its predecessors and the facts which the authors have endeavored to emphasize, namely, the interrelation and interdependence of the various divisions of the subject upon each other, are more clearly portrayed than in the second edition of 1917.

F. H. L.

THE DIAGNOSIS AND TREATMENT OF HEART DISEASE. By E. M. BROCKBANK, M.D. (Vict.), F.R.C.P.; Hon. Physician, Royal Infirmary, Manchester; Lecturer in Clinical Medicine, Dean of Clinical Instruction, University of Manchester. Fourth edition. Pp. 154. New York: Paul B. Hoeber, 1920.

THIS volume is the outgrowth of *Heart Sounds and Murmurs*, published in 1911, which was limited to cardiac auscultation. The new volume, though larger by 100 pages, is still in "pocket-book form," which makes it handy for the student's use. The first 120 pages are devoted largely to the information to be derived by inspection, palpation, percussion and auscultation in normal and especially abnormal hearts. The emphasis laid upon the insidiousness of endocarditis in children is commendable. The chapter on treatment is well considered. The medical student will find much solid information in small compass in this volume. The more mature student of cardiac disease today will prefer a volume wherein more space is given to the study of abnormal myocardial function.

J. E. T.

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PHYSICAL BASIS OF HEREDITY. By THOMAS H. MORGAN, Professor of Experimental Zoölogy in Columbia University. Pp. 305; 117 illustrations. Philadelphia and London: J. B. Lippincott Company.

OF the recent advances in the study of heredity and Mendelism, none have been so productive in results as the experimental work of Professor Morgan and his colleagues. About ten years ago they began work with *Drosophila*, the little fruit fly, and this form has turned out to be the most favorable yet utilized in the study of heredity. In *Drosophila* they have already found several hundred factors which exhibit Mendelian segregation; its chromosomes are distinct and few in number; it is both hardy and prolific; it is easily handled in the laboratory, being reared in pint bottles and fed on small pieces of ripe fruits. These advantages have been utilized to the full and the author believes that, as a result, some of the basic problems of heredity have been solved. In fact the opening statement in this book is: "That the fundamental aspects of heredity should have turned out to be so extraordinarily simple, supports us in the hope that Nature may, after all, be entirely approachable. Her much advertised inscrutability has once more been found to be an illusion due to our ignorance." The book deals with both genetics and cytology and the main thesis is the chromosome theory of heredity. According to this the chromosomes form the material basis of heredity. The various factors,

upon which the manifestations of characters depend, are resident in the chromosomes, whence they influence the nature of the cells and of the organism which the cells collectively build up. The six principles of heredity are discussed in the light of our present knowledge of the chromosomal mechanism.

Due recognition is given the valuable work of Carothers on the mechanism of assortment and that of Wenrich on crossing-over and the linear order of the material of the chromosomes. The involved portions of the discussion will appeal more to the specialized student of this subject, but there is much of interest to the general scientific reader. Those interested in the study of genetics will look forward to reports of the work being done this year in California by Professor Morgan and his associates.

W. H. F. A.

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FUNDAMENTALS OF HUMAN ANATOMY. By MARSH PITZMAN, A.B., M.D., Professor of Anatomy in the Dental Department of Washington University, St. Louis. Pp. 356; 101 illustrations. St. Louis: C. V. Mosby Company, 1920.

THIS is an attempted compromise between the compend and the modern standard anatomies, which the author describes as having grown into encyclopedias of our entire anatomic knowledge of the human body. He thinks the rank and file of practitioners of medicine show an unfortunate lack of knowledge of and interest in anatomy, and ascribes this to the attempt to teach too much detail, which results only in confusion. So he has essayed to show his own idea of a modern text-book of human anatomy.

The main point is that only those things are included which it is likely the student will remember. For instance the brachial plexus is given in half a page, and it may be contended that that is all even a fourth-year undergraduate can still retain. Still, as the author advises recourse to the drawings and plates of the larger anatomic works, one cannot be sure that he thinks that this book contains all the student should know. This book is interesting as showing one man's method of teaching anatomy to students who are beginning the study of this subject, and, undoubtedly, if more professors of anatomy would write out their actual methods of teaching it would make for the progress of anatomical pedagogy.

W. H. F. A.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Studien zur Kriegsnephritis (Studies on War Nephritis).**—THANN-HAUSER (*Ztschr. f. klin. Med.*, 1920, xcviii, 181). This article is a report on 800 cases of acute nephritis. 78.3 per cent. were edematous, 18.6 per cent. edema free and 3.1 per cent. had an edemaless nephritis following a specific infectious disease. The disappearance of the edema was rapid in 60 per cent. and slow in 40 per cent. A characteristic feature of war nephritis is the presence of pulmonary edema dependent on an edematous tendency and not on cardiac insufficiency. Bronchitis was rare but dyspnea was nearly constant at onset. Diuresis was produced by limitation of fluid and salt intake and occasionally by the use of diuretics and digipuratum. Skin drainage of 1000 c.c., often initiated marked diuresis. Fever at onset was very rare. The blood-pressure was high in nearly every edematous patient. With the disappearance of the edema the pressure reached normal. In the non-edematous patients hypertension was present in 65 per cent. The hypertension is almost without exception transient and bears no relation to the non-protein-nitrogen values. Slight cardiac enlargement with loud second sounds was not uncommon when marked dyspnea was present. Albuminuria in the early stages of the disease often reached 20 gm. After the disappearance of the edema more than a trace is unusual. Hematuria is a constant symptom. The specific gravity was high during the oliguric periods but sank when diuresis set in. Changes in the fundi were observed in only two instances. Uremic-eclamptic attacks occurred in only 2 per cent. of the cases, always just after the beginning

of the diuresis. The mortality from acute nephritis was 0.25 per cent. During the grippe epidemic, however, 10 patients, or 4.5 per cent., died. The remainder of the report concerns itself with the problem of edema, and the author concludes that "simultaneous with injury to the kidney injury to the mechanism which regulates salt and water exchange between tissue and blood occurs. Through the summation of these insults edema occurs."

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**Amyotonia Congenita and Spinal Muscular Atrophy.**—KNOX and POWERS, in an article entitled "Three Cases of Spinal Muscular Atrophy, Probably of Werdnig-Hoffman Type" (*Southern Med. Jour.*, 1920, xiii, 86), report on three instances of familial occurrence of muscular weakness in young children. The most striking symptoms were marked paresis of muscles of extremities, especially in the proximal parts, and diminution or absence of the tendon reflexes. The sphincters and muscles of deglutition were not involved. Sensation seemed normal. Two of the patients died before the third year. Unfortunately pathological study was not done. Brief mention is made of autopsy reports of other observers. As a complement of this paper an exceedingly interesting article by Krabbe, entitled "Congenital Familial Spinal Muscular Atrophies and Their Relation to Amyotonia Congenita" (*Brain*, 1920, xliii, 166) has appeared. He failed to find any instances of amyotonia congenita in adults, possibly because those who had the disease were either dead or well. He believes, therefore, that Collier is correct in assuming two different diseases in infants which may be very similar. One is amyotonia congenita and the other progressive muscular dystrophy. These two diseases differ, as shown in the following grouping: (1) Amyotonia congenita is a benign, non-heredo-familial malady with hypotonia, hyperreflexibility and weakness, but without muscular atrophy. The patients recover. (2) From this true amyotonia congenita must be separated certain reported atypical cases and also the cases which, at autopsy, showed atrophy of anterior horn cells and muscles. This group comprises the true muscular dystrophies of infancy of which the Werdnig-Hoffman type is best known.

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## SURGERY

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UNDER THE CHARGE OF

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**Lung Abscess from a Practical Surgical Point of View.**—WHITTEMORE (*Surg., Gynec. and Obst.*, 1920, xxxi, 144) says that although medical books give lobar pneumonia as the most common etiology of lung abscess in his experience it has seldom if ever been the cause. The

most common cause in his experience has been the aspiration of blood or infected matter during or following operations on the nose and throat or the extraction of teeth. The next most common cause has been bronchopneumonia. Contrary to belief the diagnosis is difficult to make. A differential diagnosis must be made between lung abscess, bronchiectasis and a small encapsulated or interlobar empyema. A careful history, sputum examination, roentgen ray, and physical examination are absolutely necessary. The roentgen ray is probably the most important, because it not only makes the diagnosis, but also pretty definitely localizes the process. Having made the diagnosis what is the correct treatment? All chronic cases should be operated on, the acute cases also unless the patient is in such a desperate condition that surgery is contra-indicated. The operative technic depends on the operator. The two-stage operation is the safest procedure to use, although it is oftentimes very much more difficult to find the abscess at the second operation. Whittemore describes his technic. The complications to look for following operation are empyema and hemorrhage, but the mortality should not be unduly high if the abscess is well localized and the correct time for operation is chosen.

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**Late Hereditary Syphilis and the Chronic Abdominal Syndrome.**—CASTEX-DEL VALLE (*Surg., Gynec. and Obst.*, 1920, xxxi, 161) say that hereditary syphilis is a very frequent cause, perhaps the most frequent, of membranous perenteritis and analogous conditions. Its pathogenesis is complex as several factors operate, which set down in chronological order are: defects of conformation in the intestinal walls because of the faulty endocrine function which presides over and governs their development. These malformations on the one hand and the abnormal function of the nervous system (sympathetic and autonomous) owing to endocrine deficiencies produce defects in the gastro-intestinal statics and dynamics; as a consequence of the latter we have intestinal stasis which brings on chronic inflammation of the colon. From the wall of the colon the inflammation spreads to the surrounding serous membrane, aggravating the existing congenital lesions. The primary cause of all this is hereditary syphilitic infection, generally in the form of a late manifestation. These cases should first be given mixed antisiphilitic treatment with mercury chiefly. The surgical treatment is not to be abandoned, but is to be restricted to cases in which definite indications confirmed by clinical and radiologic diagnoses point to mechanical alterations of importance (kinks, adhesions, etc.) or to coexisting inflammatory lesions of adjacent organs—ovaries, tubes, appendix, gall-bladder, duodenum and stomach. Surgical treatment should consist in separating the membranes and in molding and mobilizing the peritoneum, together with careful peritonization and removal of the adjacent affected organs.

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**Pseudomyxoma Peritonei.**—BIGGS (*Annals of Surgery*, 1920, lxxi, 619) feels that this condition has not received the proper recognition from American surgeons. Pseudomyxoma peritonei is the result of the rupture of a pseudomyxomatous cyst of the ovary or the appendix into the general peritoneal cavity. The ovarian origin is by far more frequent. The epithelial cells which are set free are implanted on the

peritoneum where they produce pseudomucin and tumor formation. Failure of the condition to result from rupture of a pseudomyxomatous cyst is explained by (1) the infrequency of rupture of the smaller loculi which contain cells that are active but firmly adherent to their basement membrane, and (2) thinning of the walls of the larger loculi, the cells at the point of rupture not becoming implanted easily. The symptomatology is that of increased intra-abdominal pressure. The operative findings depend upon the stage in the disease at which the operation is undertaken. Early invasion of the peritoneum is characterized by a pebbly appearance. The average age of Bigg's patients was over sixty years, this showing that the lesion is one of advanced years. In order to attempt a cure the original growth, and as much of the implanted material as possible, should be removed. Although histologically benign, the condition clinically may be malignant. If operated on early the patient may be cured and at any stage the operation may inhibit growth.

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**Sarcoma of the Stomach.**—DOUGLAS (*Annals of Surgery*, 1920, lxxi, 628) reviews the subject of gastric sarcomata and reports three cases. One per cent. of gastric tumors are sarcoma. The average age of patients suffering from this condition is 41.6 years, while that of carcinoma is 61.2 years. The earliest form to develop is the lymphosarcoma. This and the round-cell type are the most common forms. Although they are liable to be infiltrating the round-celled type may form pedunculated intragastric tumors. The round-celled variety results more frequently in ulceration, but this is not as common as in gastric carcinomata. The spindle cell and myxosarcoma are liable to form large exogastric tumors. Statistics show that the most common site is the pylorus, but the pylorus is less often attacked by sarcoma than by carcinoma. The diagnosis cannot be made with certainty. The metastasis is less rapid than in carcinoma, so that the operative prognosis is better. A gastric tumor with x-ray findings in a patient below the cancer age, the absence of blood in the gastric contents and stools, free hydrochloric acid and an absence of cachexia plus an anemia, points toward a diagnosis of sarcoma. The author reviews 230 cases besides the three he reports.

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**A Case of Cancer of the Pancreas.**—KOETLITZ (*Arch. Med., Belges*, April, 1920, p. 291) reports a case of carcinoma of the pancreas which before operation seemed to be a carcinoma of the stomach. Exploratory laparotomy was resorted to to establish a diagnosis. There had not been any jaundice or steatorrhea. The palpable tumor seemed to be a part of the stomach and the pain seemed to point to that organ. The pain, however, was not related to the patient's meals and was worse at night. Laparotomy and later autopsy confirmed the diagnosis of adenocarcinoma of the head of the pancreas.

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**Clinical Consideration of Osteomyelitis.**—OCHSNER and CRILE (*Surg. Gynec. and Obst.*, 1920, xxxi, 263) say that osteomyelitis practically always has its origin in the medullary tissue, although at times it may originate beneath the periosteum and also as Iyars says: "Frequently there are two foci, one subperiosteal and one in the medulla." Early

and concise diagnosis and immediate surgical treatment are of the greatest importance. The operation should invariably consist in splitting the periosteum for a distance of 2 to 5 cm. beyond the area of pain upon pressure in the bone in each direction. In extremely severe cases this should be the extent of the primary operation. In less severe cases ultimate healing can be hastened by carefully opening the medullary canal at the point previously located because of pain upon pressure. Care should be employed to prevent traumatizing the tissues by rough chiselling. Moist hot antiseptic dressings with fixation of the extremity and with the use of electric light treatment increases the comfort and facilitates healing. The shaft of a long bone should never be removed until a good involucrum is formed. In late cases or in secondary operations upon cases treated as above in the acute stage, every particle of dead tissue must be removed. At this operation some definite plan must be carried out to facilitate closing the defect. Skin grafting is of great value in many cases. Local foci of infection such as abscesses of tonsils or teeth or sinuses, should invariably be eliminated at once upon undertaking the treatment of patients suffering from osteomyelitis.

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**The Treatment with Radium of Cancer of the Bladder.**—KELLY and LEWIS (*Surg., Gynec. and Obst.*, 1920, xxxi, 303) say that cystoscopy has entirely altered all former methods of diagnosis as well as treatment. Of the various causes of blood in the urine, a bladder tumor is the commonest. For three reasons radical excision cannot always be the method of choice; the operation may be impossible on account of the site and extension of the growth. The operation is formidable and dangerous, considerations of age and physical condition having weight, and again it is followed by recurrence with notable frequency. Beer's use of the high frequency current for benign papillomatous growths frequently yields brilliant results. In a large percentage of the cases the growth is on the trigonum, which also prohibits any attempt at removal. In radium we have an effective means of treating at least some of these malignant growths of the bladder. After the patient is cystoscoped and the bladder distended with air, the radium on the end of a sound is placed close against the tumor. As a rule the emanation equivalent of a gram of radium is used for three to ten or more minutes. Such treatments can be given from one to four times in a fortnight. As a rule the application of radium checks the bleeding promptly. The infiltrative type of bladder cancer can, in a woman, be cross-fired from the vagina. A third method of treating these growths is to implant a capillary glass tube containing emanation directly in the tumor. Usually 5 cm. or more of emanation is imbedded and permanently left in place.

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**The Effects of Radium Emanations upon Brain Tumors.**—FRAZIER (*Surg., Gynec. and Obst.*, 1920, xxxi, 236) reports three interesting cerebral lesions treated with radium emanations. Frazier points out several ways in which malignant brain tumors differ from malignant tumors of other organs: (1) they do not metastasize; (2) they frequently grow very slowly; (3) distinguishing feature of brain tumors is that the cardinal symptoms, headache, vomiting, and visual disturbances are attributable often not to the presence of the tumor but to secondary



ventricular distention; and (4) the inaccessibility of the growth on one hand or the absence of localizing signs on the other. Radical brain operations are prohibitive in all tumors except those distinctly encapsulated. Because of these many reasons there is a field for some physical agency which will not only arrest the growth of the malignant lesion, but even lead to a process of retrogression. Frazier in coöperation with Pancoast has used radium in the treatment of 24 cases of brain tumors. He reports 3 cases where the evidence points to an arrest and in all probability a destruction of the tumor. One of these cases was a pontile angle tumor, 1 a cerebellar tumor and 1 a pituitary tumor. Frazier considers radium therapy of importance especially in the latter cases following a sellar decompression. Frazier and Pancoast advocate direct implantation in the growth when feasible.

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**The Jones Operation for the Ankylosis of Subdeltoid Bursitis.**—BLANCHARD (*Jour. Orthoped. Surg.*, 1920, cii, 466) says that subdeltoid bursitis is one of the most common and at the same time most frequently unrecognized of shoulder-joint injuries. The diagnosis is difficult in the first month. Blanchard reports a typical case with cure. The patient was anesthetized and held on an operating table so that the scapula rested securely upon the table. The assistant's fist was placed in the axilla so as to prevent a dislocation of the head of the humerus. The arm was moved firmly into abduction and rotated inward and outward and then pushed backward to its normal limit. Then the arm was given forcibly its full radius of movement. The breaking of the adhesions sounded like the fracturing of bones. Two days later the patient had normal function. The breaking up of the adhesions should not be done in a half-hearted way. This method is to be used only when the painful fixation is due a sterile deposit of lime salts.

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**Recklinghausen's Disease with Surgical Complications.**—CALDWELL (*Surg., Gynec. and Obst.*, 1920, xxxi, 242) reports two cases of this disease. The author includes fibroma molluscum, neurofibroma, and plexiform neuroma under this title. The conditions he thinks may be due to an endocrine disturbance. Von Recklinghausen's disease should be regarded as a local manifestation of a general or constitutional vice. These patients are often of a low mentality and are often freakish. Besides the tumors of the skin a pigmentation suggestive of Addison's disease may be present. Psychoses are present in a number of cases. Tumors of the peripheral nerves and less frequently of the central nervous system are found. Skeletal changes and muscular dystrophies are common. Tuberculosis is not an infrequent complication. There is a tendency for the cases to belong to the family type. Sarcomatous degeneration of the myxosarcomatous may occur in the neurofibromata. Neurovascular changes may occur. Neurofibromata are the most conspicuous of the lesions needing surgical interference. They are multiple and are disseminated over various peripheral nerves. The plexiform neuromata are less common and may be found in the central nervous system. Pain and interference of function may also warrant surgical interference.

## PEDIATRICS

UNDER THE CHARGE OF

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**Foreign Bodies in the Air and Food Passages.**—GRAHAM (*Am. Jour. Dis. Children*, February, 1920) thinks that it is a reasonable conclusion that foreign bodies in the food and air passages are much more common than is generally believed. The statistics show that about 66 per cent. of the cases occur in children. The period of latency which follows the violent dyspnea and choking attack, and later the gradual onset and chronic character of the symptoms, might lead one to suspect the presence of a foreign body. These are certainly often overlooked. The symptoms vary greatly. The peanut kernel immediately sets up a severe laryngitis, tracheitis and bronchitis. In the peanut cases the older child may survive the acute symptoms, but nearly always develops pneumonia. Metal objects may remain in the lung for a long while and do but little harm. It must be remembered that some foreign bodies do not cast a shadow on the plate. The location of such a body may often be diagnosed by allowing the patient to swallow a capsule filled with bismuth. The roentgen ray will show the bismuth-filled capsule held in position in the esophagus by the foreign body. Patients should not be allowed to cough in the hope of expelling the foreign body. This rarely happens. The physical signs and symptoms vary according to the composition, form, shape and size of the foreign body. Suspicion of a foreign body should be aroused by the following: An unexplained leukocytosis, localized symptoms in one lung that do not clear up under treatment, no tubercle bacilli in the sputum and a gradual failure in strength and weight. Bronchoscopy should be performed as soon as possible. There is no contra-indication except extreme weakness in the patient. In this case time should be allowed for the patient to react. In children no anesthetic is necessary. Roentgen ray should always be used. The asthmatic wheeze when present is a sign of the greatest importance.

**The Effects of Deficient Diets on Monkeys.**—McCARRISON (*British Med. Jour.*, February, 1920) records experiments made on monkeys. Ten were fed on autoclaved rice and four on autoclaved rice plus butter. Twelve monkeys fed on rice, banana, monkey nuts, milk, onions and bread served as controls. The rice was autoclaved at a temperature of 130° C. for an hour and a half. An exclusive diet of rice so autoclaved may be considered to be wholly deprived of accessory food factors of all three classes, that is to say, that while excessively rich in starch it is deficient in fats, proteins and salts. A dietary of autoclaved rice plus butter is lacking in accessory food factors of the "B" and "C" classes, while it is ill-balanced with respect to proteins, carbohydrates and salts. The results of these experiments confirm those previously recorded by this observer in the case

of pigeons fed on similar food. They may be regarded as applicable in kind if not in degree to human beings subsisting on food similar in composition to that on which the monkeys were fed. Monkeys fed exclusively on autoclaved rice lost weight at the average rate of 18 grams a day. Those fed on autoclaved rice plus butter lost weight twice as rapidly or at the rate of 37.5 grams a day. As the animals were not weighed daily but only at the commencement and the finish of the experiments the averages given were approximate. It is probable that the loss of weight was much more rapid at the close than at the beginning of the experiment. The monkeys which received butter died much more rapidly than those which received none; the former in the average of fifteen days; the later in an average of twenty-three and four-tenths days. The sex of the animals appeared to have influenced the results to some extent, but the figures are too small to justify a definite conclusion. Dietaries which are deficient in vitamins and in protein, and at the same time are excessively rich in starch or in fat or in both, are potent sources of disease and especially of gastro-intestinal disease. An excess of fat in association with a deficiency of "B" vitamins and protein and superabundance of starch is especially harmful to the organism. Certain dietetic conditions greatly favor the entrance into the blood and tissues of bacteria. This is especially the case when deficiency of vitamins and protein is associated with an excessive intake of starch. Since life cannot be maintained in the monkey on a dietary almost wholly devoid of "B" vitamins, it would seem that complete absence of this vitamin from the food is of less practical importance from the standpoint of disease production in human beings than its subminimal supply. Complete deprivation of "B" vitamins, especially if there is also imperfect balance in other essential food requisites, leads to rapid dissolution and death; the subminimal supply of this vitamin will lead to slow dissolution and death. The results given in this paper may explain the great mass of ill-defined gastro-intestinal disorders and vague ill health which forms such a high proportion of the human ailments of the day.

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**The Etiology of Arthritis Deformans in Children.**—BYFIELD (*Am. Jour. Dis. Children*, February, 1920) reports ten cases. It was interesting to note that there was a uniformity in the constitutional signs and symptoms, the chief ones being emaciation of varying degree, anorexia and irregularity of temperature rising to 100° to 103°. A leukocytosis of from 11,000 to 25,000 was present. On admission to the hospital enlargement of the spleen was never found. A positive tuberculin test was seen in only one case. A rheumatic history was obtained in a few cases, but in only one instance was more than one member of the family similarly affected. The teeth were examined in every case and in only one were they found to be diseased. Blood cultures were taken in two cases and were negative. The disease tended to have its onset in the larger joints, usually the knee or the ankle, while the bones and articulations of the wrist were affected later. In two cases the condition remained monarticular for a long period of time, suggesting tuberculosis of the joint. These cases resemble the group which are commonly referred to as rheumatoid

arthritis. One case gave a positive Mantoux reaction and a diagnosis of Poncet's disease might have been considered. After two operations of the sinuses, which was followed by a subsidence of the joint swelling and pain, the inference was that there was arthritis deformans in an individual suffering with tuberculosis. The chief cause of this condition is from chronic infection in the tonsils and adenoids and accessory sinuses of the nose. In children under three years of age the portal of infection seems to be limited to the tonsils and adenoids. After this time removal of the tonsils and adenoids is not effectual in arresting the progress of the disease. A sinus infection should be suspected as an etiological factor if, after the tonsils and adenoids are removed, there remains elevation of temperature, leukocytosis, poor appetite, together with a slowness of the joints to become less painful and swollen. Relapse and exacerbations are definite indication of the need of nasal treatment. From the case mentioned previously he thinks that Poncet's disease is nothing more than arthritis deformans in an individual with tuberculosis. Although supportive and orthopedic measures are helpful, surgical treatment of the nasal sinuses is to be considered as the most important therapeutic agent. As for the prognosis it is good as far as arrest of the disease is concerned, but the deformity and functional disability may persist for a considerable period.

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**Pneumonia in Infancy and Childhood without Physical Signs.**—FREEMAN (*Arch. Ped.*, January, 1920) in this paper reports three cases in which the lesion was present, but gave no physical signs. Such cases, he says, have been previously called central pneumonias. He is strongly of the opinion that in children a positive diagnosis of pneumonia can be made without the presence of physical signs in the chest when there are several of the following symptoms present: Fever, overactivity of the *alae nasi*, a pneumonic type of respiration with a pause at the end of inspiration accompanied by expiratory grunt, a relationship between respiration and pulse approximating 1 to 3, and particularly if there is the added sign of rigidity of the upper extremities, an effort on the part of the child to protect a sore chest. Since the adoption of the routine use of the roentgen ray in hospital cases, pneumonia has been found when no physical signs of its existence have been found, and even after its demonstration by the roentgen ray and the determination of the pneumonia subsequent physical examinations have proved entirely negative. It seems important, therefore, to demonstrate, as far as possible the existence of such cases without physical signs, in view of the fact that at present it is often difficult and impossible to obtain satisfactory roentgenograms of sick children in private homes. There is an urgent need for a roentgen apparatus which can be used in private houses without the great expense now involved in such work.

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**Auriculoventricular Heart Block in Children.**—EYSTER and MIDDLETON (*Am. Jour. Dis. Children*, February 1920) report a case of partial auriculoventricular dissociation developing in a child aged two years, apparently associated with an acute nasal and throat infection.

This child had been under observation for two years. The cardiac condition is that of a well-compensated mitral lesion, associated with a 2 to 1 auriculoventricular block, with a ventricular rate between 50 and 60. The child has developed normally and at the time of the report was in apparent good health and is normally active. A search of the literature has revealed twenty reported cases of heart block in children. Nearly all of these were definitely or probably of congenital origin or occurred during the course of a severe and usually fatal diphtheria. This case is regarded as of special interest, because of its origin and the relatively mild clinical disturbance produced by the condition.

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**Scorbutic Beading of Ribs.**—HESS and UNGRE (*Am. Jour. Dis. Children*, May, 1920) remind us that for many years beading of the ribs has been regarded as a sign characteristic of rickets and as really pathognomonic. The authors noted that in a study of rickets beading varied not only in degree but also in kind. Beading of the ribs may be due to scurvy. The difficulty of concluding in a case of scurvy that beading is scorbutic is that possibly rickets may be present as a complication. The writers have had exceptional opportunity to see cases in which beading developed in spite of the fact that infants had been receiving adequate amounts of cod-liver oil for long periods. In three cases not only marked beading, but enlargement of the epiphyses as well, developed, although the babies had been receiving cod-liver oil for a period of four months or more. Further proof of the scorbutic character of these lesions was the fact that both the beading and the enlarged epiphyses were reduced markedly in size within six weeks after giving orange-juice. Canned tomato is also recommended as an antiscorbutic. Scorbutic beading occurs in animals. This has been noted by many who have produced experimental scurvy. Beading also occurs in beriberi and pellagra. It is evident that the fact that beading of the ribs may be likewise of scorbutic origin has clinical and diagnostic significance. Unless it is certain that a baby has received an adequate amount of antiscorbutic food we are not justified in considering the enlargement of the costochondral articulations as of rachitic origin. The rosary may be of two-fold nature, as these two nutritional disorders frequently coexist. This does not imply that the same defect in diet produced both, for it is known that a small quantity of fruit juices will prevent scurvy but not rickets, and, on the other hand, that cod-liver oil will generally prevent the development of rickets but has no prophylactic value for scurvy.

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**The Antineuritic and Growth Stimulating Properties of Orange-juice.**—BYFIELD, DANIELS and LOUGHLIN (*Am. Jour. Dis. Children*, May, 1920) undertake to show that orange-juice has properties of benefit to artificially-fed children other than its antiscorbutic action. It is generally conceded to be a mild cathartic, although this has been denied by Gerstenberger, who contends that its action is constipating. The diuretic action has been noted by Gerstenberger and also by Hess. It has been used in marasmus by Gladstone combined with apple-juice. Oranges and fruits in general, although valuable antiscorbutics, have not been regarded as sources of the antineuritic vitamin. The results obtained in this study by the addition of orange-juice to or the

omission of orange-juice from the diet of babies was uniform and constant. Under the conditions, maintained growth, as evidenced by weight curves, was in all cases stimulated when orange-juice was administered. On the other hand orange-juice from which the antineuritic vitamin had been removed was without influence. The fact that the changes produced were usually apparent within a day made the results more significant. That other constituents of orange-juice, as for example, the carbohydrate, played no part in the results was shown in one case. Dietary increases, both during and after an orange-juice period, were without marked effect. Furthermore, the addition of 3 gm. of sugar was also without an appreciable effect. In some cases the gains were less marked than in others, the greatest gains having been made in those babies receiving the most food, based on their theoretical weight. If the caloric intake per kilogram fell to ninety or therabouts there was less stimulation. Up to the present studies dealing with the influence of the antineuritic vitamin on growth have not shown whether the weight increases were due to the stimulation of appetite, and thus an increased ingestion of food, or to the direct influence of the antineuritic element upon metabolism. While this study does not attempt to solve this problem the observations were made with this point in view. In no case was a loss of appetite apparent, the same amount of food being taken during the entire course of the experiment. In animal experiments the conditions are quite different and the appetite is greatly diminished, so that when antineuritic vitamin is added the effect upon the appetite is marked. It appears to these observers that the appetite factor plays only a minor role in the stimulating effect of the water-soluble vitamin on growth provided a nearly adequate amount is being given. The question as to whether the antiscorbutic vitamin has growth-stimulating properties has not been the subject of expensive experimentation. It has been reported that receiving it showed better weight gains. The observations of this study fail to bear this out. There is little information regarding the coexistence and quantitative relationship in foods of the two water-soluble vitamins, the antineuritic and the antiscorbutic. Orange-juice has been shown to contain both in appreciable amounts. Tomato, banana, cabbage, potato and turnip also contain both in demonstrable amounts.

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**The Intestine in Small Children.**—ROBBIN (*Am. Jour. Dis. Children*, May, 1920) measured the intestines and body length in 185 children at postmortem. He found that the length of the large intestine was between 80 and 130 per cent. of the length of the body in 91.3 per cent. of the cases. The small intestines were 500 to 900 per cent. of the length of the body in 79.9 per cent. of the cases. An unusually long large intestine was not accompanied by an unusually long small intestine, and an unusually short large intestine was not accompanied by an unusually short small intestine. There was no association of an unusually short or long small intestine with the clinical condition causing death. There was no correlation between an unusually short or long large intestine and the clinical cause of death. An unusually long intestinal indigestion or chronic constipation. The body grows somewhat more rapidly in length during early life than either the small or the large intestine.

## OBSTETRICS

UNDER THE CHARGE OF

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**Gangrenous Appendicitis Coincident with Labor.**—GRATTIN (*Surg. Gynec. and Obst.*, November, 1919) publishes an interesting and extraordinary case: The patient was a primipara, who, upon examination, had no abnormal physical conditions. By reckoning the child was expected at the latter part of the month of October. July 15 of the same year her physician was summoned to relieve epigastric distress, which was increasing. There was slight nausea, but no pain. Alkalies and carminatives failed. Gastric lavage and an enema were given, which greatly improved the patient's feelings for two days. There were no labor pains and no abdominal pain. On the following day deep pressure revealed abdominal tenderness in the right lower portion. A lesser degree of tenderness could be found in the left iliac region. The patient had symptoms of beginning labor. Appendicitis was diagnosed and an operation was performed. The pregnant uterus was high in the abdomen and could best be reached by an oblique incision four inches in length, and necessitating a high and extremely lateral incision. When the peritoneum was opened several ounces of a slightly turbid fluid escaped, and this fluid seemed to be of general distribution. The uterus was held to one side while the operator explored the gall-bladder region, finding a tense, fluctuating and sausage-shaped mass near the cecum. This was very carefully delivered through an abdominal incision and was found to be a completely gangrenous appendix, distended with fluid, but not perforated. The proximal half-inch was still firm enough to ligate, and after being crushed with the clamp the pedicle was tied with catgut. The appendix was removed without accident. Drainage was employed after the operation and very careful closure of the abdomen was practised. The appendix was readily removed and the abdomen closed without drainage. On examining the appendix it was fusiform in shape, dull on the peritoneal surface and contained about two drams of foul, sanious pus. The appendix was in a stage of gangrene, but fortunately a rupture had not yet occurred. The tissues had been under a very great strain. When labor developed the patient was kept under the influence of morphin during the early part. In the second stage she was delivered under partial narcosis by forceps without difficulty. There was very little laceration. The placenta came away normally, but the child suffered from apnea, requiring artificial respiration and the use of the lung motor. The cyanosis diminished and respiration finally became established. This occurred two and a half hours after the birth of the child. Respiratory paralysis, however, developed, with attacks of apnea, and the child died. At autopsy he examined the baby by catheter, examining the urine for traces of morphin, thinking that perhaps the doses of morphin administered to the mother before and after the removal of the appendix might have had an influence; the

forceps could be eliminated as a cause of the fatal death and the child evidently perished from toxemia. The mother apparently did well, but then developed an irregular pulse, for which digitalis was given intravenously, and the drip method was kept in constant operation. A condition of shock developed and very free stimulation was necessary to cause the patient to rally. The intravenous injection of medicine seemed to be of direct avail. The patient's toxic condition continued, with attacks of heart failure and a gradual increase in the secretion of urine. There was considerable fever without peritonitis. On the sixteenth day after operation, after the patient had been taken home from the hospital, she developed a temperature of 104°. This continued for two days, without pain. Vaginal examination revealed nothing, and there was no pain in the wound. On the twenty-second day pain was described along the crest of the ilium to the outer side of the wound. Under anesthesia the finger was gradually introduced by stretching the tissues at the drainage-point of the wound and the index finger was inserted. There was a big sanguinous exudate to the outer side of the wound. The peritoneum seemed firm and healed and the exudate was broken up with the fingers and a rubber tube inserted. The temperature dropped and remained normal for three days. The wound gradually healed, and when the patient was discharged the pelvic conditions were found to be normal, without residual pelvic exudate. The salient points in this case are the simultaneous occurrence of labor pains, with abdominal symptoms ending in appendicitis. The appendix was totally gangrenous and greatly distended, and there was a beginning peritonitis. The baby was at full term, but died seven hours after delivery, with attacks of apnea, and finally failure in the action of the heart. The mother narrowly escaped death from postoperative toxemia, the functions of the kidney and heart being very difficult to maintain. Jaundice followed this and showed the effect of the toxemia upon the liver. The patient finally made a complete recovery. The reviewer had an experience somewhat resembling the above case which illustrates how insidious is the course of appendicitis in parturient women: A multipara, giving a history of good, general health, became toxic during her second pregnancy, and labor was induced successfully. Mother and child did well and the mother nursed the infant and went from the hospital to her home. During the week following she was taken with high fever and indefinite pain in the right lower abdomen. Purgation relieved her symptoms and her condition seemed practically normal. There was tenderness on deep pressure, but very moderate fever and general improvement. A leukocytosis of 20,000 was found, and in spite of the patient's comfortable, general condition operation was considered imperative. Pelvic examination revealed nothing. At operation a very large gangrenous appendix was found, the inflammation having extended to the right broad ligament to such an extent that when the right Fallopian tube was brought up it separated from its origin and attachments in the hands of the operator. The appendix was removed and found to be gangrenous. Although it had not, so far as could be seen, perforated, the entire right lower abdomen had become infected. Very free drainage was employed by using two large rubber tubes with gauze packing around them. This was gradually removed, the patient ultimately making a good recovery. The most careful search through the



history of the patient failed to reveal evidence of a distinct attack of appendicitis at any time during her life. During her pregnancy she had been in very good, general health until the development of toxemia just before delivery.

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**Myomectomy during Pregnancy.**—FARMAR (*Med. Jour. Australia*, May 10, 1919) records the case of a patient three months pregnant who suffered greatly from intense pain in the right iliac region. After incision the mass was shelled out, leaving a fairly deep crater, but not exposing the uterine cavity. The muscular walls of the cavity were closed by catgut mattress sutures and then the peritoneal cuff was inverted and closed by a continuous Lembert suture of cotton thread. The abdominal wall was brought together in the usual manner. The tumor removed weighed 425 grams. The patient made a perfect recovery and subsequently gave birth to a healthy boy.

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**The Legal Aspect of Operating on a Pregnant Woman for Supposed Tumor.**—In the *Journal of the American Medical Association*, July 19, 1919, is quoted a decision of the District Court of Appeal of California, First District, Division 1, affirming a judgment against a physician for having, as was alleged, negligently and without occasion therefor, performed a surgical operation on a married woman, aged twenty-two years. The patient alleged in her complaint that the physician informed her that she had a tumor in the Fallopian tube and that he operated upon her for its removal. As a matter of fact she was pregnant and five months later gave birth to a child weighing nine and a half pounds. The patient testified that when she first called the physician she told him that she had been having severe pains in her back and head and also in the pelvic region, was having scanty menstruation for almost a day each month and informed him that another physician had said he thought she was pregnant five or six weeks. The patient also testified that after the operation she heard the physician say that he had made a mistake and that she had heard others make the same statement. In the defence the physician testified that in addition to the symptoms which the patient described she told him that she had been having hemorrhages between menstrual periods and had some dizziness, that she did not suspect herself to be pregnant and that her condition then was nothing like what it had been with her first child. That so far as the history of the case went she might have had a fibroid tumor. That her condition was serious and required an operation and that an incision of about two and a half inches was made, when the diagnosis of normal pregnancy was established and the wound was closed and the abdomen dressed. Against the physician it was urged that he should have kept the patient under observation perhaps for six weeks before operating, when a correct diagnosis could have been made. As regards the necessity for operation experts testified that immediate operation was indicated only when there was hemorrhage between regular periods and that otherwise the patient should have been kept under observation until a diagnosis could plainly be made. The District Court held that if the jury in the first trial believed, as apparently it did, the testimony of the patient as to what she told the doctor relating to the history of the case then the operation was unnecessary and the original verdict

against the physician should be allowed to stand. As the patient closed her case without introducing expert evidence the counsel for the physician moved for a non-suit, arguing that the mere statement by the physician to the patient and her mother that he had made a mistake in diagnosis was not sufficient to establish negligence in the absence of testimony that such incorrect diagnosis was arrived at by reason of negligence. Assuming this to be true it was sufficient that evidence was introduced later in the case which tended to supply this defect and it did not appear that this evidence injured the physician.

**Full Term Ectopic Pregnancy.**—ROLLS (*Am. Jour. Obst.*, July, 1919) reports the case of a young primipara in the twenty-second week of gestation. At six weeks a catheter or sound had been introduced, and this was followed after several days by considerable bleeding and the discharge of clots. An abortion was thought to have occurred, but four days before coming under observation the patient's abdomen suddenly became larger. When examined the uterus was symmetrically enlarged and the fundus just above the umbilicus and the placental bruit could be distinctly made out. The natural diagnosis seemed to be an intra-uterine pregnancy further advanced than the history indicated. Five months later, and very near full term, the patient was again seen and found to be in good condition. About a week previously she had pain over the gall-bladder, with nausea, vomiting and constipation and the vomiting of small quantities of highly colored urine. The patient was slightly jaundiced, and this was unrelieved by catharsis, diet and colonic irrigation. The temperature was  $101^{\circ}$ , pulse 144 (weak and irregular), respiration 30 and difficult. Palpation revealed a firm mass extending from the upper left quadrant of the abdomen to the umbilicus, and this gradually became an indefinite cystic mass. There was well-marked dulness on percussion in the flanks. Just below the umbilicus, in the left side, a fetal heart was heard and below this a placental sound. On vaginal examination the cervix was displaced to the left and the finger could be passed only to the internal os. There was a cystic mass behind the cervix, with an indefinite firmer mass above and to the right and below the level of the internal os. There seemed to be a small fetal part which could be made out. A provisional diagnosis of full term pregnancy with toxemia, complicated by incomplete rupture of the uterus or twisted pedicle ovarian cyst. Examination at the fifth month was thought to rule out ectopic pregnancy. After being in the hospital about half a day the patient was considerably better. The fetal heart could not be heard nor were fetal movements obtained. Improvement continued, the blood showed 10,400 white cells and the patient was without pain. At consultation the opinion was advanced that probably full-term ectopic gestation was present. Six days after coming to the hospital abdominal section was done, and as there had been considerable vaginal bleeding the vagina was packed without introducing the sound into the uterus. Bloody serum escaped and the fetus was found, showing distinctly through the thin sac. This was adherent to the omentum, large intestine and parietal peritoneum, while its pedicle was in the region of the left broad ligament. The sac was opened and a full-term child and amniotic liquid were removed. When the adhesions were broken up the pedicle was at the side of the left tube and extended to the uterine horn, but did not involve the fundus of the uterus. By

clamping the tissues the placental membranes were removed, with small loss of blood. The uterus was about the size of a four months' pregnancy and had been carried backward, upward and to the left. The pedicle was secured with ligatures and sutures, portions of membrane were removed from the omentum, intestines and peritoneum, with very slight hemorrhage. The abdomen was closed without drainage, the patient making an uninterrupted recovery. The child was macerated, weighing nine and a quarter pounds. It was mature, with no deformity. The placenta had two portions, and on the embryonal side a very short, thick pedicle, which when examined by the microscope showed edematous smooth muscle. Autopsy on the child revealed a transudate of serum in the abdominal, pleural and pericardial cavities.

**Pregnancy Complicated by Volvulus of the Sigmoid Flexure, with Intestinal Obstruction.**—DONALDSON (*British Med. Jour.*, December 13, 1919) describes the case of a primipara, aged thirty-six years, thirty-seven weeks advanced in pregnancy. The patient had always suffered from constipation, but had been fairly well during pregnancy. Recently she had slipped in the street, recovering herself without actual falling, and had after this a pain in the side which she thought came from a muscular strain. Three days later, as the bowels had not acted, she sought medical help. When the physician saw her she had intermittent pain, and he examined her to see if labor had begun. There was no evidence of this, and she was treated with laxatives and enemata and without the passage of flatus or fecal matter. Two days later she was sent to St. Bartholomew's Hospital. On admission pulse and temperature were normal and there was no vomiting, and the patient did not look badly. Pregnancy was present, but in addition over half of the abdomen was very much distended. There was general tenderness and the upper part of the uterus was covered by distended bowel and the uterus pushed to the left. The position of the fetus was normal and there was no obstruction of the pelvis. At operation free fluid was found in the abdomen, and on examination this was sterile. As the uterus was at term it was pressing upon the intestines to such an extent that the operator performed Cesarean section and after this had been done the uterus could be kept out of the abdomen and the intestines examined. The pelvic colon, transverse colon, with a large loop of small intestine, were greatly distended. There was a volvulus of the sigmoid flexure, involving also a large loop of small intestines. The volvulus had one and a half twists, the bowel was untwisted and considerable time was given to emptying the colon through a rectal tube. As the patient's condition was critical the abdomen was closed without anchoring the colon to the abdominal wall. The patient and her child made an uninterrupted recovery.

**Labor; Shoulder Presentations.**—IPPOLITO (*Gazz. d. Osp.*, 1919, xl, 137) quotes the statistics of various countries regarding the frequency of shoulder presentation: Italy, 1.40 per cent.; Austria, 0.71 per cent.; France, 0.66 per cent.; Belgium, 0.59 per cent.; Germany, 0.58 per cent.; England, 0.36 per cent.; United States of America, 0.35 per cent. The writer has practised for twenty years in Sicily and in 10,000 labors; he has seen 150 cases of shoulder presentation. Among his patients contracted and deformed pelvises are not uncommon.

## GYNECOLOGY

UNDER THE CHARGE OF

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**Radium Treatment of Carcinoma of the Uterus.**—From April, 1914, to October, 1919, 165 cases of carcinoma of the uterus were subjected to radium treatment by SCHMITZ (*Wisconsin Med. Jour.*, 120, xix, 157), and for the purpose of study of the clinical value of radium therapy, he has divided the cases into five groups: Group 1. Cases which were clearly operable after a physical examination. Group 2. Cases which were doubtfully operable: (a) cases subjected to surgery and ray therapy, and (b) cases subjected to ray therapy only. Group 3. Cases in which an operation was absolutely impossible: (a) cases subjected to abdominal hysterectomy and ray therapy; (b) cases subjected to vaginal cautery and ray therapy; (c) cases subjected only to ray therapy. Group 4. Cases so far advanced that all treatment was hopeless, which were subjected to ray therapy for purposes of palliation. Group 5. Cases that recurred after an abdominal panhysterectomy. A study of the results obtained demonstrates at once the importance of early diagnosis and treatment. We can hope for cure or improvement in cancer statistics only by instituting measures resulting in an earlier recognition and immediate proper treatment of these carcinomata. The clearly operable cases made a remarkable and favorable showing. There were two deaths in a total number of 12 cases treated. The living cases have gone from one to five years without any sign of recurrence. In Group 2, 20 cases were treated. Of these 13 were subjected to operative and ray therapy. Of these 7 are living while 6 either died or did not report. Of the 7 cases treated only with rays 5 are living and 2 died. It is impossible to state whether an operation should have been performed or not as the cases are too few and too recent to permit a conclusion. However, it appears to Schmitz that surgical eradication does not materially influence the results for the worse. It is not surprising that Group 3 presented the largest number of cases, namely 73. Of these 16 cases were subjected to hysterectomy either before ray therapy was begun or after a local healing was obtained with ray therapy. The results were disastrous. Only two patients have survived the ordeal. Twenty-one cases were subjected to an initial vaginal cautery before radium was applied. Three patients survive to date, while the average duration of life in those known dead is twelve months. On the other hand, 11 of the 37 patients treated only with radium therapy are well at the present writing. The duration of life of those that died in class (a) is nine months, in class (b) twelve months, and in class (c) twelve

months. In other words the patients in the latter class had a better chance all around than those in the former class. We must conclude that if local healing is obtained, the tumor is arrested in growth and the infiltration of the parametria subsides, we should not subject the patient to an unnecessary operation. This conclusion of Schmitz is in entire harmony with our own belief which is based upon our experience with this class of cases as seen in our service in the University of Pennsylvania Hospital and which dictum we have been emphasizing for several years. Group 4 demonstrates one fact. An advanced cancer patient should be treated only with ray therapy to relieve the symptoms as this is all we can hope for, but even then little benefit is obtained for the efforts spent. The intensive intermittent plan of treatment cannot be carried out in this class of cases as the rapid generation of tissue invariably causes a severe auto-intoxication. A period of from four to eight days should intervene between applications, that is until the reaction has subsided. Group 5 shows a few brilliant therapeutic results. Recurrent carcinomata are very refractory to radium treatment. Comparing this group with groups 1 and 2, Schmitz deduces that a combination of surgical treatment and ray therapy shows such favorable results that surgical eradication of carcinomata must always be combined with an intensive ray treatment. If we procrastinate and postpone the latter until recurrences appear, and they do appear in about 75 per cent. of the cases within the first two years following the operation, then ray treatment also cannot improve the outlook in the majority of cases. It is his opinion that the sooner after operation the recurrence takes place the better the palliation from ray therapy.

**Treatment of Calculi Impacted in Lower Ureter.**—Many surgeons still appear to be under the delusion that directly a shadow of a stone in the lower ureter has been shown by roentgen-ray examination, they should immediately cut down and try to remove the stone. Nothing is more fallacious than this idea, states KIDD (*British Med. Jour.*, 1920, July 31, p. 160), which has led to many disasters. Experimental work on animals to determine how long a stone can lie in the ureter before damaging the corresponding kidney irreparably suggests that six months to a year is the longest time during which a stone ought to be allowed to obstruct the ureter. But from clinical evidence Kidd is convinced that such experimental work does not reveal the whole truth. In the first place, stones rarely block the ureter completely, so that natural conditions differ from many of the experimental conditions. In the second place, clinical evidence suggests that the kidney may recover sufficiently to do much useful work, even if the ureter has been partially blocked for many years by a stone. Provided then, that there are no imperative indications for operative interference, Kidd believes that it is advisable to give the patient one to two years in which to pass a ureteric stone naturally, aiding Nature by minor cystoscopic manipulations. The methods in use today for coaxing a stone down the ureter are: (1) Injection of sterile oil through a ureteral catheter around the stone, which may induce it to pass in a few days. (2) Injection of 5 c.c. of a 4 per cent. solution of papaverin sulphate locally into the ureter through a catheter. This alkaloid causes direct relaxation of unstriated muscle fiber, relaxing the ureteric muscle in the region of the

stone and has been successful in causing stones to pass. (3) Incision of the superior wall of the mouth of the ureter by means of the operating cystoscope and the special Lewis scissors, starting from the mouth of the ureter and cutting through the bladder wall for at least three-quarters of an inch. Following this, the ureter may be dilated and possibly the stone can be grasped and extracted. The slit in the ureteral mouth heals without stricture formation. Although Kidd has found it necessary to operate upon twenty-eight patients suffering from stone in the lower ureter during the past ten years and has only lost one case, nevertheless he wisely counsels reasonable delay in resorting to surgery and the employment of cystoscopic methods during such delay, if the best interests of the patient are to be served.

**Radium in Benign Type of Bleeding.**—CURTIS (*Wisconsin Med. Jour.*, 1920, xix, 172) briefly summarizes his experience with radium therapy in bleeding from the uterus due to non-malignant conditions. There were 62 fibroid tumor cases which were subjected to the ray therapy. These were selected cases because the tumors were of moderate size and nearly all of the cases were treated for hemorrhage. Myomectomy or hysterectomy has thus far been given preference in younger women, in tumors of large size, and in cases with other pelvic lesions. Except in a very few instances no attempt was made to avoid bringing on the menopause and the treatment consisted of curettage with the intra-uterine application of 50 mc. of radium for a period of twenty to twenty-four hours. The hemorrhage always stopped but the decrease in the size of the tumor has varied considerably. Subsequent hysterectomy has been resorted to a few times because of symptoms from preëxisting pressure or adhesions. The menopausal symptoms, which sometimes occasion much annoyance, have been controlled by fresh corpus luteum or ovarian residue, especially the latter. The hemorrhage has invariably been controlled in the 81 cases of myopathic bleeding of the menopause which were treated. Under the term "idiopathic hemorrhage," Curtis includes those patients, who, in the absence of gross pathological changes, suffer from excessive flow during the child-bearing period. Most of such cases are ascribable to physiological disturbance of, or pathological interference with the ovarian function. Many of these patients dread artificial menopause, and delicate management is required to preserve menstrual function. For example, in a given case menorrhagia may be due to psychic disturbances which produce chronic pelvic congestion. Treatment with radium decreases the menstrual flow to normal. Thereafter, if the cause of functional disturbance is removed amenorrhea may follow. Again, women in the upper thirties, particularly unmarried women, are prone to menorrhagia. Sometimes the bleeding is a precursor of the menopause and certain of the patients are not relieved with moderate doses of radium. Others are particularly susceptible and the menopause is unexpectedly ushered in. Still, again, small doses may have no appreciable effect. After two or three applications the flow may increase rather than diminish. Another treatment is given and the menopause follows. The increased flow was a warning of an impending menopause. Two patients with idiopathic hemorrhage may react quite differently. Equal applications may cause a return of normal menstruation in both

cases, but two years later one may have a return of menorrhagia while the other may go on to early menopause. Certain facts are helpful in the management of these cases: Organotherapy occasionally makes radium unnecessary. If radium is used an amount in excess of 1000 mc. may induce the menopause especially in women over thirty-eight years. Increased flow after treatment suggests a possible menopause as does also an increase in blood-pressure. From the standpoint of ultimate results it is preferable to give repeated small doses, *e. g.*, 300 mc., at intervals not more frequent than once in three months, without control observation of blood-pressure and subjective symptoms.

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**Hemolytic Streptococci in the Throat in Certain Acute Infectious Diseases.**—OTTERAAEN (*Jour. Infect. Dis.*, 1920, xxvi, 23) examined the mouths, noses and throats of three hundred patients, most of whom had either diphtheria or scarlet fever, to determine the prevalence of hemolytic streptococci. Surface inoculation of goat's blood-agar plates was employed, although a higher percentage of positive findings was encountered when the enrichment method was used. While all organisms produced complete hemolysis the surface colonies varied considerably as to size and intensity of hemolysis. According to Holman's classification most of the fifty strains tested were either *S. pyogenes* or *anginosus*. Animal inoculations and phagocytosis experiments indicated that the organisms isolated were not virulent. Of the 300 cases, 46.6 per cent. showed hemolytic streptococci on admission and some became positive after entrance, making a total of 60 per cent. In the patients with diphtheria, positive cultures were obtained in 10 per cent. from the nose and 4.6 per cent. from the mouth, whereas in the scarlet fever cases the nose cultures were positive in 20.8 per cent. and the mouth in 12.8 per cent. Only a small number of patients yielded positive cultures from all three sources, the mouth, nose and throat. Those with positive nasal cultures, as a rule, had negative throat findings, and *vice versa*. When hemolytic streptococci were present in the nose, they were often predominating, while in the mouth they were usually found in small numbers. Negative cases which later became positive frequently did so after being in contact with carriers.

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**The Fate of Streptococcus Hemolyticus in the Gastro-intestinal Canal.**—Pathogenic streptococci, especially hemolytic streptococci, gain access to the gastro-intestinal canal from the throat and tonsils where they have been shown to occur in normal individuals as well as by the ingestion of certain foods, particularly infected milk. While the strong

bactericidal effect of gastric contents on bacteria in the stomach is recognized and while hemolytic streptococci occur in normal feces in relatively few instances, little is known of the specific action of the intestinal juice on the *Streptococcus hemolyticus*. In an effort to ascertain the action and fate of hemolytic streptococci in the alimentary canal, DAVIS (*Jour. Infect. Dis.*, 1920, xxvi, 171) introduced into the stomachs of three rabbits, by means of a catheter, 10 to 20 c.c. of one avirulent and two virulent strains of these organisms. Each type of organism was fed for ten days to each of the animals, during which time daily examinations of the feces were made. It was found that hemolytic streptococci did not occur normally in any appreciable number in the gastro-intestinal canal of rabbits. When introduced into the stomach of rabbits these bacteria may occasionally pass through the canal and appear in the feces. At the end of thirty-one days the animals were sacrificed and examination of the gastro-intestinal canal at various levels indicated that the hemolytic streptococci did not develop to any great extent in the intestines, not did they readily gain a permanent foothold there. From additional investigations it was observed that rabbits with generalized streptococcus infections in joints and blood showed none of these hemolytic streptococci in the intestinal contents; that the gastric juice of normal acidity from man and rabbits killed hemolytic streptococci in from two to five minutes, while gastric juice in achylia may not kill them in several hours; that hemolytic streptococci were not found in the normal human feces of 53 cases and that hemolytic streptococci, when mixed with normal human feces lived in the icebox for several days, whereas in the incubator they tended to die out rapidly.

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**Relation of the Portal Blood to Liver Maintenance.**—ROUS and LARIMORE (*Jour. Exper. Med.*, 1920, xxxi, 609) carried out a series of observations upon the liver following upon the partial occlusion of the portal vein. Rabbits were used in the experiments. They found that it was quite easy to completely shut off a large part of the portal circulation, leaving, however, a sufficient distribution to the right posterior and caudate lobes to maintain adequate liver function. As soon as the one branch of the portal vein is ligated the involved lobes become smaller and dark in color. In the meantime the mass of portal blood is diverted to the remaining branch and the lobes supplied by it become swollen and of brighter color. Hypertrophy of the latter lobes begins within three days and by the end of twelve days has more than doubled in size. Subsequently it slowly increases and eventually reaches the size of the entire original liver. A process of atrophy continues in the ligated portion, the lobe gradually dwindling to a shrunken fibrous mass. The connective tissues of the stroma do not show response either of the nature of replacement fibrosis or of inflammation. By these experiments three-fourths of the liver may be reduced to a fibrous tag within two months. The bile which is secreted from the liver mass advancing in atrophy is almost colorless and deficient in bile salts. The authors suggest that the results of the experiment should aid in an understanding of certain chronic liver lesions. It is indicated that the portal blood bears a relation to the liver not only for its functional capacity but also more directly for its vital support.



**The Mycelial and Other Microorganisms Associated with Human Actinomycosis.**—COLEBROOK (*British Jour. Exper. Path.*, 1920, i, 197) gives a series of 27 cases of actinomycosis, 17 in the years 1911-14 and the remainder since the war period. These were all true types of *Actinomyces bovis*, all showing suppurative lesions with visible granules in the pus and 25 per cent. of these showing clubs at the periphery of the granules. For purposes both of diagnosis and culture, actual granules were obtained from the pus. He first deals with the mycelial organisms isolated and later with the associated bacteria. He classifies the first into groups *A*, *B* and *C*. Twenty-one strains came in group *A*. These strains were filamentous organisms, being slender branching and seldom straight for more than 20 or 30 microns. They were Gram-positive but not acid-fast and showed a strong preference for anaërobic growth. Cultures were obtained on ordinary nutrient agar or broth but grew better with 1 per cent. glucose. Their viability was slight (60° C. for one hour killing the cultures). He identified this strain with the *Actinomyces bovis* of Wolff and Israel. Group *B* included two strains. They were similar to *A* in their preference for anaërobiosis, slight viability and morphologic features. However, they grew poorly on glucose agar and no aërobic cultures were obtained. Group *C* included one strain. The mycelium was perhaps straighter but otherwise similar to *A*. Cultures gave a single aërobic colony. Subculture on glucose agar gave several large flat rosettes which grew deeply into the media. The three remaining cases were not sufficiently worked out to be grouped. The author opposed the idea that the ray fungus was derived from grasses and vegetation, inasmuch as it is an anaërobe. He is more inclined to believe that it is a frequent inhabitant of the alimentary tract and from there is carried into the tissues. Coarse agglutination with the serum of heavily infected persons occurs up to 1 in 500 to 4000 dilutions. Similar results were obtained in sera of rabbits inoculated with a vaccine of *Actinomyces bovis*. In 30 cases, the granules of which were examined, 24 showed an associated organism having the following characters: coccoid forms or bacilli; no capsules; non-motile; Gram-negative; star-like colonies that adhered to the tube in fluid cultures; grew aërobically or anaërobically; viability slight (52° C. for half-hour kills); pathogenicity for man was not determined but for animals doses 300 to 15,000 millions produced death. He identified this organism with the *B. actinomycetum comitans* described by Klinger while working in Zurich. The author advanced four hypotheses trying to solve the reason for the presence of these organisms in over 80 per cent. of his cases. None of these, however, seemed satisfactory to himself. Other organisms, such as streptococcus and staphylococcus, may be found in the cervicofacial and abdominal cases of actinomycosis.

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**The Pathological Histology of Tonsils Containing Hemolytic Streptococci.**—KELLERT (*Jour. Med. Res.*, 1920, xli, 387) disparages the growing tendency to attribute the source of systemic infections to the tonsils, stating that, though these organs may often harbor pathogenic bacteria, it is by no means a corollary that these lymphoid masses are therefore the initiators of the general disease. He further notes that an abrasion must be present on the mucous surface of the tonsil to provide a portal of entry for the infecting material, and yet many

ulcerated tonsils have been removed from adults who have previously manifested no distant affections. It is noteworthy, also, that the investigator through his own work and that of others, notably, Smith and Brown, Smillie, Nichols and Bryan, and Tongs, has been led to conclude that streptococci carriers are as definite and menacing an entity as are those of typhoid, dysentery and diphtheria and to this list must also be added meningococci and pneumococci carriers. The work in the various army cantonments with epidemics of hemolytic streptococci infections strengthens this conclusion. The author examined the material bacteriologically only for hemolytic streptococci. Seventy pairs of tonsils were cultured and examined microscopically. Cultures were made from both the mouths and from the depths of the crypts near the capsules. It is of significance to note that the greatest numbers of hemolytic streptococci were grown from the cultures taken in the depths of the tonsils. The figures for the frequency of finding hemolytic streptococci in these seventy instances are not presented. Grossly, the tonsils varied considerably in size and shape and all those showing hemolytic streptococci presented a more or less constant microscopical picture. No abscesses were encountered. The capsules were generally thickened with the branching trabeculae showing a correspondingly denser structure. Old blood pigment, muscle and mononuclear cells were seen in the fibrous capsule. The writer feels that no analogy can be safely drawn between the chronicity of infection and the density of the capsule. Ulcerations of the mucous surfaces of the crypts with a penetrating infiltration of polymorphonuclear leukocytes and mononuclear cells were observed. Bacteria were present to a greater or less degree in all the crypts. The lymphoid follicles were hyperplastic and less definite in outline than normally. Cartilage was found in the capsule of 10 per cent. of those positive for hemolytic streptococci, and in 25 per cent. of those not showing this organism. The investigator's views are summarized in a terse manner wherein he observes that infected and diseased tonsils are not infrequent in healthy adults and that the largest tonsils are not necessarily the most severely infected. Inflammatory changes indicative of infection may be found in nearly all tonsils. The conclusion is drawn that hemolytic streptococci may be saprophytic in the tonsil and that no distinctive pathologic lesion can be assigned to this organism in the tonsil.

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**Observations on Changes in Virulence of Hemolytic Streptococci with Special Reference to Immune Reactions.**—NAKAYAMA (*Jour. Infect. Dis.*, 1920, xxvii, 270) observed the changes in virulence of hemolytic streptococci produced by animal passage, growth in artificial culture and certain other conditions, at the same time noting the reactions with immune serums of streptococcal strains of varying degrees of virulence. It was found that the virulence of a streptococcus rapidly decreased on artificial cultivation, particularly on blood agar. The amount of peptone in the medium apparently did not influence the virulence so much as the reaction, acid reaction maintaining virulence better than alkaline. The virulence persisted longer under anaërobic than aërobic conditions. An avirulent streptococcus increased in virulence for both rabbits and mice on passage through the rabbit. When also passed through mice, the virulence was further increased, particularly for mice and when a certain maximum of virulence had been reached no further increase

developed on further passage through the mice. When the maximum virulence for mice had been established passage through rabbits sometimes increased virulence for rabbits but decreased for mice. On the other hand, if virulence for mice was still increasing, passage through rabbits could increase the virulence for both rabbits and mice. By keeping streptococci in a collodion sac in the rabbit peritoneal cavity, it was found that virulence may be increased. In the agglutination reactions, cinnabar was employed to obviate the action of minor agglutinin and to prevent spontaneous agglutination of the streptococci. It was learned that the agglutinability of a streptococcus may change as the result of animal passage, the particular strain used for immunization being agglutinated more strongly than the related strains by the corresponding immune serum. The original non-virulent strain of streptococcus was agglutinated by all the immune sera. The same relation seemed to obtain with reference to opsonins and phagocytosis, as well as with respect to specific precipitation and conglutination, but no difference between the different strains by means of complement fixation could be made out. All the various strains were agglutinated in the same way by acid solution.

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**Noma in the Dog.**—Fusiform bacilli and spirilla are so universally found in the morbid tissues of noma, Vincent's angina and other phagedenic processes that, in light of our present knowledge, most writers believe that we are justified in considering them as the possible if not the probable causative agents in these processes. PHILLIPS and BERRY (*Jour. Infect. Dis.*, 1920, xxvii, 136) report typical noma in a dog, a cocker spaniel, which developed after a mild attack of distemper. The lesion began on the right lower lip and extended to the ramus of the jaw and tissues of the neck. Prostration ensued after eight days, death occurring on the thirteenth day, when the moribund animal was killed after pneumonia developed. Daily smears from the lesions, stained by dilute carbol-fuchsin, showed that *B. fusiformis* and spirilla greatly predominated over a small number of micrococci and short bacilli. In the later stages of the disease, the fusiform bacilli tended to form involution forms which frequently resembled thick spirilla. Attempts to culture the organisms anaërobically on glucose horse serum agar were unsuccessful. Smears from the gums of normal dogs showed only a few fusiform bacilli and spirilla. The authors suggest that dogs be used in experimental noma and call attention to the possibility of contagion from dogs to man.

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**Studies in Epidemic (Lethargic) Encephalitis; Cultural Studies.**—In previous communications, Strauss, Hirschfeld and Loewe have reported the findings of a filtrable virus in cases of epidemic encephalitis. Later, a filtrable organism obtained from the virus by special cultural methods, was described. LOEWE and STRAUSS (*Jour. Infect. Dis.*, 1920, xxvii, 250) have reviewed the previous work, supplementing additional studies. The organisms appeared to thrive best when the original Noguchi technic was followed, employing sterile kidney fragments and ascites fluid medium. The optimum solid medium was gelatinous in character, consisting of nutrient agar, ascitic fluid and kidney tissue. Cultures made on ordinary media and by Rosenow's technic have proved negative. A minute filtrable organism has been cultivated from

the brain, nasopharyngeal mucous membrane, nasopharyngeal washings, spinal fluid and blood of epidemic encephalitis cases, while control cultures of material from human patients suffering from or dead of conditions other than epidemic encephalitis were found to be uniformly negative. Under dark field illumination, the organisms were minute, globular, refractile, non-motile forms, occurring singly in diploform chains and clumps, the latter form predominating. Young cultures on fluid media were Gram-positive, while the older ones and those on solid media appeared to be Gram-negative. Tinctorially, the organism was of a basophilic nature. The same organism has been recovered from the brain and nasopharyngeal mucous membrane of animals which were inoculated with virus or culture and which succumbed to the experimental disease. The cultures thus recovered have produced the disease when injected into other animals and the organism has again been recovered. Positive animal inoculations have been obtained with the eleventh generation of this organism. Berkefeld and Mandler filtrates of brain material, nasopharyngeal mucous membrane and washings, spinal fluid and blood from cases of epidemic encephalitis have produced in rabbits and monkeys lesions typical of the disease. The virus has been passed through many series of animals and can be preserved for months in 50 per cent. glycerol. The authors suggest that their results indicate that epidemic encephalitis can be differentiated from epidemic poliomyelitis since rabbits are susceptible to the infectious material of the former and not to the latter, and monkeys are very susceptible to poliomyelitis and relatively refractory to epidemic encephalitis. Again, spinal fluid from poliomyelitis is innocuous to rabbits and monkeys, whereas spinal fluid from cases of epidemic encephalitis produces lesions typical of the disease in both these animals.

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#### A Study of Streptococci Obtained from the Mouth in Cases of Chorea.

—The triad of articular rheumatism, endocarditis and chorea and their frequent association with streptococcic tonsillitis have furnished problems for repeated investigation, and further since the streptococcus has been shown to be the organism most commonly isolated in the group, lends added interest to the study of the streptococci found in the mouths of chorea patients. FLOYD (*Jour. Med. Res.*, 1920, xli, 467) details his findings in the study of the streptococci obtained from the mouths of 26 individuals clinically manifesting chorea. Previously Mayer and Cole were able to produce acute arthritis and endocarditis in animals by the intravenous injection of streptococci obtained from various sources but only Beattie reports symptoms suggestive of chorea following the intravenous injection of streptococci and these were not typical. Westphal, Wassermann and Malkoff, Apert, Richter and Poynton and Paine isolated a diplococcus from cases of chorea and the latter were able with their diplococcus to produce choreiform twitchings, arthritis and endocarditis in rabbits. The author is impressed by the infrequent positive findings from blood cultures in definite cases. In the present instance cultures were taken from about the teeth and from the crypts of tonsils in 26 cases of acute chorea and planted upon Loeffler's blood serum or blood agar. The streptococcus was readily isolated from all but 3 cases. Blood cultures were negative as were the cultures of cerebrospinal fluid. Pure cultures of the streptococci were introduced into the peritoneum of mice and if fatal to the animal within twelve to twenty

four hours, subcultures were taken from heart's blood and joints and rabbits were inoculated intravenously. From 1 to 6 inoculations were required to produce fatal results in different animals and when death ensued immediate autopsy was performed and subcultures of organisms obtained from definite lesions were perpetuated for possible later therapeutic use. In 4 cases definite vegetative endocarditis was developed in the rabbit and the infective organism in three of these was from tonsil while the fourth was from teeth. Eight animals manifested acute swelling of joints with definite crippling. The brain of the animals showed only engorgement of the pial vessels. Ten children with healthy throats were cultured as control cases and from only three of these were streptococci grown and not one of these was pathogenic for the mouse. An attempt was made to determine some method for therapeutic usage of the virulent organisms. However, in all attempts the results proved negligible. The author was able to prove satisfactorily that members of the streptococcus group may be isolated from the pathological lesions in endocarditis, articular rheumatism and chorea. He found also that the percentage of virulent streptococci about the teeth and in tonsils of chorea patients is much higher than in normal throats.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**Possibilities of Using Mosquito Traps in Antimalaria Work.**—METZ (*Public Health Reports*, 1920, xxxv, 1974) states that the control of malaria is rapidly becoming a rural problem as the expensive mode of eradication applicable to urban communities cannot be applied to country districts under present economic conditions. The writer noted that *Anopheles* were attracted by pigs and a pen was devised which served as a trap, allowing the mosquito to enter but not to emerge. It is suggested that a chemical agent might take the place of the pig and that the whole subject is worth full study.

**Necessity of Low Temperatures for the Preservation of Vaccine Virus.**—The Public Health Service (*Public Health Reports*, 1920, xxxv, 1762) publishes a warning against keeping vaccine virus under unfavorable temperature conditions. It is pointed out that the virus should be kept in contact with ice during the summer period and at a low temperature at all times. Special refrigerating devices are recom-

mended for shipment in hot weather. Vaccine virus should not be carried in the doctor's vest pocket. A few hour's summer heat may destroy the viability of the vaccine. The chief cause of negative takes during the summer season is failure to keep the virus cold.

**Mosquitoes and Bats.**—It appears according to HOWARD (*Public Health Reports*, 1920, xxxv, 1789) that the insect-devouring habits of bats are being employed to reduce the mosquito nuisance in some sections of this country. The warning is issued that this method of mosquito control is on a purely experimental basis and not to be depended on unless further controlled work shows the practicability of this method.

**Soaps in Relation to Their Use for Hand-washing.**—NORTON (*Jour. Am. Med. Assn.*, 1920, lxxv, 302) states that sterile hands are not obtained in the ordinary process of hand-washing. More bacteria were found to be removed by the ordinary toilet soaps than by the special soaps. In other words the cleansing properties of a soap are more important than its "germicidal" or "antiseptic" constituents. The soap solutions obtained in hand-washing are of no practical germicidal or antiseptic value. The soap left on the hands after washing has no germicidal action. In the whole process of hand-washing done in the usual manner the special so-called "germicidal" or "antiseptic" soaps exhibit none of these properties. Therefore, these terms are not proper to use in connection with soaps. Finally, since the hands may serve as a medium for the conveyance of bacteria in infectious diseases it is important to remove these bacteria; this may be done by the ordinary toilet soaps as effectively, if not more so, as by the special brands of so-called "antiseptic" or "germicidal" soaps.

**The Value of Prophylaxis Against Venereal Diseases.**—MOORE (*Jour. Am. Med. Assn.*, 1920, lxxv, 911) states that the low annual incidence rate of venereal disease during the war was due to several factors which have been discussed in recent communications. The various methods employed, however, would have accomplished less satisfactory results had it not been for the use of prophylactic measures. During 1918-19, as consultant urologist to the District of Paris, the writer was able to study the results of prophylaxis on a large scale. He states that Ashburn concludes that the measures employed in combating venereal disease were effective in this order: (1) Those that keep men chaste; (2) those that diminish the opportunities for sexual contact, especially efforts at the suppression of prostitution; (3) those that diminish the dangers of contact, especially venereal prophylaxis; (4) those that exact punishment. The method of prophylaxis used was as follows: Under no circumstances was a patient (even an officer) allowed to administer the treatment to himself; it must always be done by the attendant. If for any reason the attendant was unable to employ the treatment exactly as directed, he must state the reasons therefor and the deviation adopted on the prophylactic record. As a first step the patient was instructed to urinate. Then he was provided with a pint of warm water in a basin and a gauze wipe, with which he washed thoroughly, while the attendant

dropped liquid soap on the penis. An examination of the genitalia was made; if the patient had a discharge or a genital sore the fact was noted on the record and the patient instructed to report to the clinic; but this was as far as the attendant was allowed to go in making a diagnosis. He must continue the treatment as usual. The next morning, on receipt of the records at the clinic, all such records were separated from the others and the commanding officer of the patient's organization requested to have him report for examination at once. The next step was the injection of 1 dram of a 2 per cent. protargol solution (freshly made twice a week and kept in a closely stoppered bottle to avoid deterioration) into the urethra by the attendant. The patient then held the meatus firmly between the thumb and forefinger for five minutes, from time to time allowing a drop to escape from the meatus, so that all parts of the urethra were in contact with the solution. At the end of five minutes, the protargol was allowed to escape without pressure, so that a few drops remained. One-half dram of 33 $\frac{1}{3}$  per cent. calomel ointment was next rubbed thoroughly by the patient, under the observation of the attendant, into all parts of the penis for five minutes, special attention being paid to the retracted prepuce, the frenum and the glans. Finally the penis was wrapped in toilet paper to protect the clothes and the patient instructed not to urinate for four or five hours. Throughout, the strictest precautions as regards sterility of syringes by boiling was maintained to prevent transfer of infection from one patient to another. So far as the district of Paris was concerned the use of the prophylaxis was the largest single factor in the prevention of venereal disease. With Ashburn's figures on the relation of exposure to disease as a basis for argument it is estimated that 2571 new cases of disease were prevented. The method of prophylaxis described is calculated to make the treatment more efficacious. The statistics presented show that prophylaxis is 99.6 per cent. efficient in the circumstances under which Moore employed it. Prophylaxis is probably equally efficacious against all three venereal diseases.

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**High Incidence of Typhoid in Small Epidemic.**—LEAKE and MESSER (*Public Health Reports*, 1920, xxxv, 2197) observed an epidemic of typhoid fever due to an infection of a salad served at a banquet at which 49 among 90 diners developed the disease, making an incidence of 54 per cent. Many cases were atypical and a considerable number occurred among persons who had been vaccinated against typhoid or who had previously suffered from the disease. The source of infection was a woman in the early stages of typhoid fever who had prepared the mayonnaise dressing used on the chicken salad.

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**A Comparative Study of State Regulations for the Control of Influenza.** FEEZER—(*Public Health Reports*, 1920, xxxv) collected data on the subject discussed by means of a questionnaire and presents the following summary of conclusions: (1) Great divergence of practice exists on practically all features of influenza control as represented by the regulations and other measures which are in force throughout the country. (2) It is noticeable that 97.5 per cent. of the forty states considered require some system of reporting. The reports are made to the local health officer in 74.4 per cent. of these states; to

the state health officer in 12.8 per cent.; and to both in 12.8 per cent. The method is the same in 92.3 per cent., namely, by mail. (3) There is a great division in practice in quarantine methods, also in regard to placarding. (4) A noticeable fact with regard to the closing of public places in time of epidemic is a tendency to shift the responsibility to the local health authorities. A number of comments which were received in addition to the straight answers to the questions indicated a growing inclination to the view that closing is useless. (5) On the matter of public funerals the practice is fairly equally divided. (6) Relative to the use of serum, it is very clear that public health authorities, almost without exception, are unwilling to undertake the responsibility of making any recommendations whatsoever.

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**Studies of Reconstructed Milk.**—STEVENSON, PECK and RHYNUS (*Public Health Reports*, 1920, xxxv, 2011) present the following summaries of the study: Under manufacturing and handling: (1) Reconstructed milk and cream made from skimmed milk powder, unsalted butter, and water have been produced in large quantities at Nitro, W. Va., and sold to the public. (2) The cost of manufacturing these products in the Southern States is less than the cost of local normal milk. As the distance between the points of efficient production and consumption is lessened, this difference in cost becomes less. In the dairy sections at the present time fluid milk can be sold more cheaply than reconstructed milk. (3) Reconstructed milk products serve as excellent emergency supplies, and as soon as the process of manufacturing milk powder is perfected they will no doubt compete in the open market with normal milk products. Under the analytical study: (1) Studies of the bacterial content of this plant's output of reconstructed milk and cream show that it was satisfactory from a health standpoint. (2) It has been demonstrated that satisfactory ice cream can be manufactured on a commercial scale, with a bacterial content comparable to that of well-pasteurized milk and cream. (3) Using the revolving coil type of ice-cream batch mixer for mixing the ingredients entering into reconstructed milk, a product of homogeneous fat content cannot be made, and the final product from an entire batch should be mixed before bottling.

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**Sunlight in the Sterilization of Tuberculous Sputum.**—TÉCON (*Paris méd.*, 1920, x, 33) placed sterilized sand, gravel and dust on a terrace with southern exposure at Leysin, Switzerland, and dropped upon it sputa from consumptive patients, previously examined for tubercle bacilli. Meteorologic data were recorded at short intervals throughout the experimental period. Sputa thus exposed to the mountain sun in the summer for periods of from two to over fifty-two hours—the experiment in the latter case extending over nine days—all gave positive results when subsequently inoculated into guinea-pigs; in some instances, however, the onset of tuberculous disease was considerably delayed. All the experiments but one were conducted in cloudless weather. In another series of tests sputum was exposed to the sun on beaten snow. In these tests the sputum was regularly rendered sterile in less than twenty-nine hours. The marked discrepancy between the temperature by day and night in this series is thought to have been



a factor in the sterilization, but there are other possible factors, such as reflection, ultraviolet rays, etc. In one experiment sputa from the same patient and with approximately equal bacterial content were exposed simultaneously on snow and on the above mentioned reproduction of an ordinary footway. After twenty-three hours of isolation on the latter medium the sputum gave positive results in guinea-pigs, while after like exposure on beaten snow inoculations were negative. This shows that the difference between temperatures by day and night cannot be the sole factor in the more rapid sterilization upon exposure over snow. The general conclusion from the experiments is that the sterilizing value of sunlight on tuberculous sputum discharged upon public highways is practically negligible in the summer time; it is more marked on sputum discharged on mountain roads during the snowy season.

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**The Effect of Shaking Alkalinized Aqueous Solutions of Arsphenamin and Aqueous Solutions of Neoarsphenamin in the Presence of Air.**—ROTH (*Public Health Reports*, 1920, xxxv, 2205) showed experimentally that shaking solutions of arsphenamin and neoarsphenamin in the presence of air led to marked increase of toxicity of the drugs. Preparations which are difficultly soluble should, for this reason, not be shaken as a dangerous increase in toxicity may result. Warning is given against preparing solutions in a mortar or large beaker as is sometimes practised.

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**Bacteriologic Characteristics of Tubercle Bacilli from Different Kinds of Human Tuberculosis.**—GRIFFITH (*Jour. Pathol. and Bacteriol.*, 1920, xxiii, 129) states that the main objects of his investigations were (1) to determine by the examination of unselected cases the relative proportions of the human and bovine types of tubercle bacilli in different kinds of human tuberculosis, and (2) to ascertain the frequency of occurrence and the distribution in the human body of variant strains of tubercle bacilli. Of 1068 persons examined, 803 showed human bacillus infection, 194 bovine bacillus infection, and 5 a mixed infection. Of various regions involved the examination showed that bovine infections occurred as follows: Bones and joints, 19.7 per cent.; genito-urinary organs, 17.65 per cent.; cervical glands, 46.3 per cent.; meninges, 20 per cent.; scrofuloderma, 34.65 per cent.; lupus, 48.9 per cent. As to the age periods, bovine infection occurred as follows: During the first five years of life, 37.55 per cent.; from five to ten years, 29.45 per cent.; from ten to sixteen years, 14.66 per cent.; after sixteen, 6.25 per cent.

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